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FILM REACTIONS AS A NEW APPROACH TO BIOLOGY¹

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TOWARDS the end of the last century the biologist and physiologist were agreed that the biological entity was the whole living unit. This century has seen an attack on biological problems by the physical and organic chemist. The study of the living unit has been dropped and in its place we find investigations on specialized processes such as oxidation and reduction or catalytic reactions. It is an unfortunate fact, as the late Sir William Hardy clearly pointed out, that in this method of approach the mechanism of the coordination or the integration of the activities of an assemblage of cells must remain insoluble. It is this very point which I think deserves some consideration. We know for example that at death the catalysts escape from control since the molecular structure of the mov-

ing parts gets disorganized. Again, Loeb showed that unfertilized sea urchin's eggs could be made to develop by immersion in salt solutions of sufficient concentration. In development a whole series of complicated chemical reactions are set in operation and it is clear that in the quiescent unfertilized egg all the chemical ingredients for the reactions are present but await some change in organization before reaction sets in. We must conclude that the mechanism of integration is at any rate dependent on a pre-existing organization of at least the major operative portions of the assemblage of cells. This raises a number of important problems such as, what types of organization are to be found in living material; how far control over chemical reactions can be effected by modification of the type or extent of such organization and finally how far different types of organization can modify such important factors as the chemical or physical state of

¹ Address of the president of the Section of Chemistry, British Association for the Advancement of Science, Dundee, August 31, 1939.

a material or chemical equilibria in reacting systems, and lastly what new properties or reactions make their appearance as a direct result of organization.

Whilst it has been frequently stated that one of the chief characteristics of living matter is that it contains a relatively large proportion of matter in what we designate the colloidal state, a closer analysis indicates that in fact the colloidal properties of living matter are due to the fact that an exceptionally large fraction both of material and of energy is present in films, membranes, fibers, fine capillaries and the like. It thus seems pertinent to inquire a little into the properties of surfaces of separation between bulk phases or of matter in the boundary state. These surfaces of separation can be considered as a new phase—the interphase—and for our discussion we must examine this phase and find in what respect it differs from the enclosing bulk phases.

Whilst we must pay attention to the static properties such as composition, form and orientation we must not forget that it is the dynamic properties of ingress and egress, of flow and chemical action in and with the two-dimensional contents of the phase that we are particularly interested in, but any integrating features of the former are of great importance if it can be shown that they produce effects in the dynamics of the system which are not to be found in non-structural liquid or vaporous phases.

We already know that the composition of the interphase differs from that of either of the bulk phases in contact with it and the general principles governing relationship between its composition and its three dimensional partners were clearly enumerated by Willard Gibbs and Sir J. J. Thomson. Equally important are the considerations of Sir William Hardy and Irving Langmuir, who showed that in many cases when dealing with an interphase we were actually examining a monolayer—a hypothesis suggested by Lord Rayleigh. Finally we know the molecules contained in the monolayer are orientated with respect to one another and to the plane of the interphase. I need not enlarge at this point on the structure and different physical states as well as the effects of variation of the external variables on the equilibria of the phases of monolayers of simple molecules such as derivatives of both paraffinic and cyclic hydrocarbon, since these have been exhaustively examined during the last twenty years, but monolayers both of macromolecules as well as those composed of binary and components of a higher order possesses a number of interesting and somewhat unexpected properties.

We find, for example, that macromolecules such as the methylated or acetylated starches and celluloses or the native proteins can be spread as monolayers. The chains are extended at the interface and in general the non-polar side chains penetrate into one (the non-

polar) and the polar side chains into the other (the aqueous) phase. This separation of the side chains by the solvent action of the homogeneous phase can only be effected by suitable partial rotation along the chain involving the usual cis-trans motion. Thus no single protein chain can acquire along its entire length either the α or β keratin configuration unless the side chains alternate in polarity in suitable fashion. Monolayers of both the proteins and of the derivatives of starches and celluloses when suitably compressed acquire rigidity and interesting elastic properties; we are forming in fact a two-dimensional gel, the prototype of a membrane. We shall return to some of the reactions which are observed with such monolayers, but may observe in passing that these macromolecules in a monolayer are in part crossing one another by the accident of distribution, in part associate with one another through three separate factors: (a) the non-polar side chains forming a hydrophobic surface to a triplex sheet; (b) association through the $-CO-NH$ linkages in the chains; (c) association between some of the polar heads in the substrate. It appears that at extremely great surface dilutions of many proteins actual molecular separation occurs, and we are thus presented with a simple method of determining the molecular weight from the relation $FA = RT$ of these complex bodies.

We have referred to the fact that molecules in a monolayer are orientated relative to one another and to the substrate and that this orientation can be altered by extension or compression. If the molecules in the monolayer undergo reaction with a reactant dissolved in the substrate the rate of reaction may be modified by the change in molecular orientation of the former. This is equivalent to a control of the steric factor and determining the path of approach of a reacting molecule or ion to the reactive portion of the other reactant. In this way both the reaction velocity and the height of the energy barrier or apparent energy of activation may be altered.

In Tables 1 and 2 and Fig. 1 are given three different examples of such a variation in reaction effected by change in compression of a monolayer.

It is interesting to observe that these film reactions can be carried out with minute concentrations of strongly adsorbed reactants. Thus in the case of the attack of lecithin by snake venom to form lysolecithin a half life of about one hour is obtained with a concentration of venom as low as 2.5×10^{-6} per cent. When cobra venom is examined by this method it is found that only in extreme dilutions does any reaction occur. This inhibition at higher concentrations is due to proteins present in the cobra venom which are absorbed in preference to the enzyme by the lecithin monolayer. Egg albumin, although not so effective when added to black tiger venom, will produce a similar result. In

In addition to lecithinase present in snake venoms, other enzymes have been studied and amongst them crystalline trypsin and crystalline pepsin which rapidly digest monolayers of caseinogen, the former at pH 8 and the latter at pH 2. When the purified and crystalline enzyme preparations are employed, these enzyme actions on the protein monolayers behave exactly as

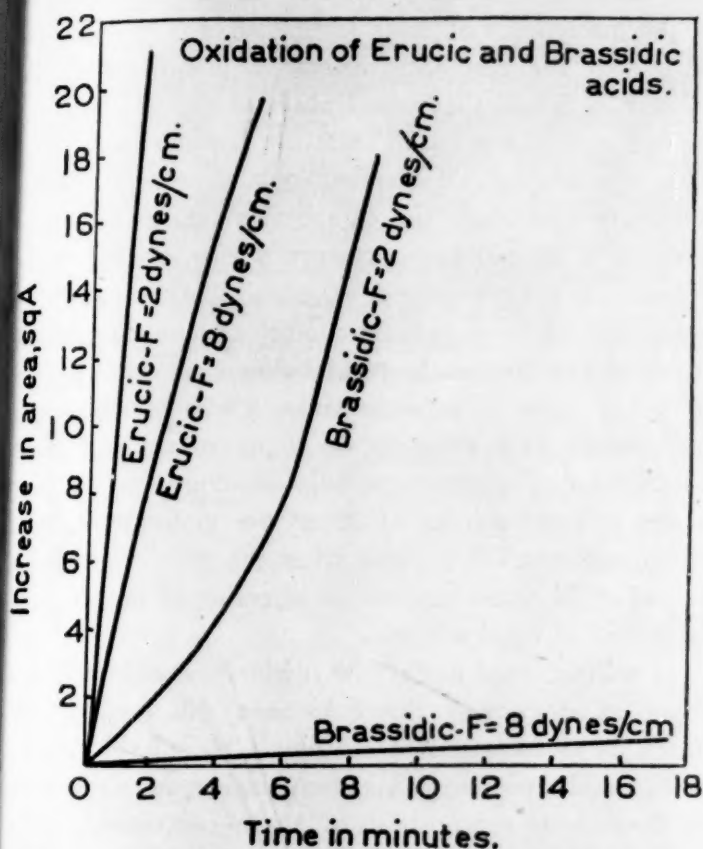


FIG. 1. Oxidation of Erucic and Brassidic acids by 0.005 per cent. KMnO_4 and $\text{N}/100 \text{ H}_2\text{SO}_4$.

in bulk phase, although the protein has undergone a process akin to denaturation. With unpurified proteolytic ferments, on the other hand, fatty acid protein complexes are invariably present which give rise to other phenomena.

TABLE 1
HYDROLYSIS OF TRILAURIN ON $\text{N}/5 \text{ NaOH}$. $T = 20^\circ$

F dynes/cm	E cal./gm mol.
5.4	10,000
10.8	13,200
16.2	16,100

In the reactions which we have discussed the chemical processes involved do not differ from those which

TABLE 2
ATTACK ON LECITHIN MONOLAYERS BY 0.001 PER CENT. BLACK TIGER SNAKE VENOM AT 20° AND PH 7.2

No. of lecithin molecules per sq. cm $\times 10^{-14}$	Half life in minutes
1.04	0.5
1.27	4
1.57	32
2.11	90

would occur in similar systems in the disorganized state, and the only effects of molecular organization into oriented monolayers are noted in the alterations produced in accessibility of the groups as revealed by the rapidity of the reactions and in the apparent energies of activation.

A further consequence of molecular orientation at interphases is found in those cases where radiation incident on the surface produces photochemical action after absorption of quanta by chromophoric groups in the monolayer. If, as is the case in ring compounds, the extinction coefficients are different along the three molecular or group axes, the photochemical reaction rate can be varied by alteration of the orientation by compression. Thus the rate of photochemical hydrolytic fission followed by oxidation in protein monolayers at those points along the chain where the chromophoric groups are situated can be varied within wide limits by simple expansion or contraction.

There are several processes in which an alteration in the properties of an interphase bring about a number of varied biological processes of great importance. I may mention the phenomena of lysis, agglutination, sensitization and the lethal activities of certain substances on various types of cells and micro-organisms. It is true that we are not yet certain in any one case as to the exact composition, structure or thickness of the cell membrane, but we are certain that the surface structure must be organized in the sense that forces of molecular orientation must be operative in the membrane. Whilst, as we have seen, a monolayer membrane of a protein may be destroyed by suitable enzymes, yet the phenomena which I am now referring to do not appear to be the result of chemical action in the usual sense of the word. The reactions themselves do not appear to possess large temperature coefficients indicative of sensible energies of activation, although it must be admitted this fact is frequently obscured by other processes operative at the same time. We may mention in passing the thermal denaturation of proteins is a reaction in which the apparent and true energies of activation are markedly different, a fact emphasized by the investigations of Steinhardt and La Mer. A second criterion is to be found in the fact that these processes are nearly all catastrophic in character, *i.e.*, the process under investigation being recorded as a hit or miss. As far as quantitative results are possible in such systems it appears that a definite quantity of reactant related naturally to the extent of all surface is required to bring about the reaction, and further that this quantity is removed from the environment on to or into the cell wall. One further point of interest is that the relation between the quantity on or in the cell wall and the concentration in the environment can be expressed in terms of an adsorption isotherm. Not too much stress may be

laid on this last point, because the adsorption isotherm may equally well be replaced for existing experimental data by a partition function between two phases or by the mass law operative between easily dissociable salts.

Whilst the extent of mutual miscibility of two liquid phases is usually interpreted in terms of the relative internal pressures of the two liquids, we note from the molecular point of view, especially in the case of the large complex and the biologically important material, that we are really concerned with specific molecular interactions which may be identified as being due to those forces operative between the non-polar and the polar portions of the molecules respectively. In two component monolayers the two molecular species are adlineated in respect to one another, and we should thus anticipate that it might be possible to form relatively stable two-component complexes which in three dimensions would only be detectable in terms of mutual solubility and when a mutual solvent was present as a third component might not be observable at all. These conclusions are indeed fully borne out by investigations on two component monolayers. It is found, for example, that strong complexes are formed in mixed monolayers of a variety of substances such as saponin with cholesterol or digitonin or cetyl amine or sulfate with cholesterol.

Examination of a great variety of these systems has demonstrated that the free energy of formation of the complex is constitutive in the sense that its magnitude is dependent on the extent of interaction between the polar reactive groups and also that of the Van der Waals interaction between the non-polar portions of the reacting species. The difference in properties of mixed films containing cholesterol on the one hand and those containing, for example, epi-cholesterol is most marked, but when models are made of the two molecular systems, it becomes quite evident that the ease of adlineation of the hydrophobic portions of the molecule and the relative orientation of the polar group with respect to the axis of the molecule are the determining factors. The free energy changes involved in formation of these two-dimensional complexes is of the order of some 10,000 cal. per gm. mol. Complexes containing the constituents in ratios other than one to one can be prepared; thus cetyl alcohol and cetyl sulfate can form both a 1:1 and a somewhat unstable complex in the ratio of 1:3, whereas elaidyl alcohol produces an unstable 1:2 but no 1:3 complex. It is probable that with a more extended investigation of these interesting systems the basis for the most elementary form, *i.e.*, a two-dimensional crystallography of the type envisaged by Patterson may be laid down.

I might mention in passing that the effects of cis-trans isomerism on the free energies of the complexes are very characteristic and fully confirm the hypothesis

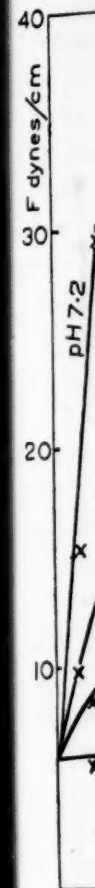
we have advanced as to the importance of molecular adlineation; thus saturated aliphatic hydrocarbon chains with different reacting polar groups will form stable systems, likewise trans-olefinic chains can penetrate and pack both with one another and with saturated chains, but the cis form is not capable of such adlineation. From the biological point of view I think that the most interesting property of these systems lies in the mechanism of their formation, for on injection of one of the reactants beneath a monolayer of the other it is found that penetration of the latter by the former will take place to form the complex monolayer. This penetration, if carried out at constant area, naturally involves a rise in the two-dimensional pressure, or if at constant pressure a rise in area is involved. We have indeed examined the formation of complexes under both these conditions, and the changes involved are frequently remarkable, thus the injection of a few mgm of saponin under a film of cholesterol compressed to a pressure of 10 dynes/cm will cause an increase of pressure of over 50 dynes/cm. Whilst a film of cetyl alcohol at 20 A² per molecule expands to no less than 78 A², even when the pressure is maintained at 23 dynes/cm on the injection of only 1 mgm in 300 cc of cetyl sulfate.

If sodium cetyl sulfate be injected beneath a monolayer of cholesterol this substance will penetrate to form, as we have seen, a complex. By suitable adjustment of the pressure this complex can be maintained at the definite composition of one to one, excess of the sodium salt being ejected as the pressure is raised. It is found that the pressure on the film has to be raised as the concentration of sodium salt in the substrate is raised; some of the values obtained are given in Table 3.

TABLE 3

Conc. sodium cetyl sulfate gms/cc $\times 10^{-1}$	Equilibrium pressure in dynes/cm for the 1:1 complex formation
1.0	17
2.0	32
3.0	38
4.0	45
5.0	47
6.0	48

We conclude that there must be a more or less complete layer of the sodium sulfate adsorbed beneath the surface of the complex. We are thus led to the view that in many oil-in-water emulsions as well as in the micellar aggregates found in soap solutions the gegen ion atmosphere around the emulsion particle or micelle must contain a number of molecules of the emulsifying soap, a somewhat novel conclusion as to their structure. Further, that emulsions formed from such complexes should be remarkably stable with a low interfacial energy. In some cases a small alteration in the pH of the substrate may affect the ease of penetration of



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a reactant to a marked extent. In the diagram is shown the effect of such a variation on the rate and extent of penetration of bilirubin into cholesterol as a function of the pH. It is possible to examine the reactivity of various substances in respect to penetration of monolayers. I have referred to the penetration of monolayers of cholesterol and we note that some substances such as digitonin or cetyl sulfate or amine possess this property to a remarkable extent. Of the other important cell wall constituents we include phospholipins and the proteins. Little information as yet is available on phospholipins, but our knowledge of the reactions of this type in the case of the proteins,

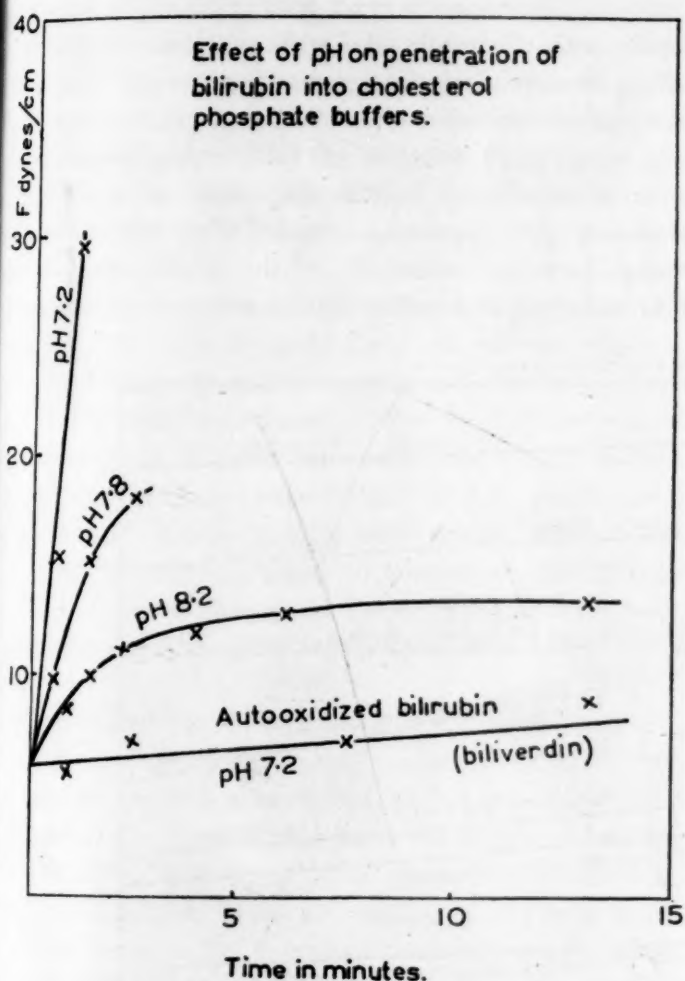


FIG. 2

especially the alcohol soluble and thus readily dispersible protein gliadin, has been greatly extended in recent years.

The stability of the protein monolayer is, as we have seen, due partly to their mutual association; if these are broken down by stronger associating reactants we might anticipate a dispersion of the monolayer resulting in a solution of the protein in the form of a protein-reactant complex. This phenomenon is readily observed on injection of even minute quantities of such substances as sodium oleate, cetyl sulfate or psychosin beneath a protein monolayer.

Other substances may react by penetration into the protein layer but not effect dispersion. By spreading

monolayers with various head groups and examining the reactions caused on injection it is possible to identify the reacting group in the protein monolayer. A characteristic group of protein complexes formed in monolayers are the lipo proteins; thus gliadin forms a remarkable complex with cholesterol in the ratio 4:1 by weight. Here the cholesterol is anchored to specific groups in the gliadin, in particular the amino and carboxylic groups. At high pressures (20 dynes) the cholesterol is forced up above the protein monolayer, and the surface becomes one essentially of cholesterol. Nevertheless the cholesterol is still anchored to specific portions of the protein, for on release of the pressure the lipo-protein film is re-formed. This extrusion and re-forming process can be repeated several times before the complex structure breaks down. It is interesting to note that saponin, which penetrates cholesterol with extreme ease, but proteins only slightly, will penetrate these lipo-protein films except at those pressures where the cholesterol is separated from the substrate by the protein monolayer to which the cholesterol is anchored.

It thus appears not unlikely that the materials such as cytoplasm, and especially in the more stratified chloroplasts, must be regarded as a protein gel framework to which is attached the enzymes, the phosphatides and lipoids and the means of attachment is as we have seen due to the interaction both of the non-polar as well as of the polar portions of the molecules concerned. Another important conclusion to be drawn from monolayer experiments is that these penetrative reactions involve not only a new head group interaction, but in many cases also the breaking of such a head group interaction already existing in the monolayer prior to penetration. Several biological analogies may be mentioned—thus since lysis of blood cells can be brought about both by protein and cholesterol penetrants we must conclude that it has lipo-protein surface. Several micro-organisms can be sensitized for lysis by cholesterol penetrants by a prior treatment with cholesterol. Again, cilia of mytilus appear to be mainly lipoidal, those of paramoecia chiefly protein, as judged by the criterion of penetration.

The carrier action of desoxycholic acid on fatty acids can readily be demonstrated in monolayers, as desoxycholic acid does not interact with other lipoids nor to any great extent with proteins. We find also that the hemolytic activity of a long chain alcohol is negligibly small, owing to the fact that it is practically insoluble in water, but it readily forms a soluble complex with a long chain sulfate and can be transported to the cell wall in this form. There both the sulfate and the alcohol can penetrate separately, the former acting both on the protein and on the lipoid, the latter only on the protein, and produce lysis.

Yet another reaction of this type has been described by Peters and Wakelin, who found that the complex

ovoverdin containing protein and astacin could be split to form a lipo-protein containing soap by the addition of small amounts of saturated long chain fatty acids setting free the astacin. On the addition of calcium ions the process is reversed. They likewise draw attention to the fact that it seems probable that the co-enzyme in an oxidase system may be separated from the enzyme by the formation of such a lipo-protein complex.

Somewhat more complex in behavior are the blood coagulants heparin and the synthetic sulfate celluloses. It is found that their biological activities run parallel to the ease with which they penetrate films of cholesterol. It is not unlikely that they operate by breaking down a cholesterol cephalin complex, setting the latter free.

We have referred to the fact that for the penetration of a monolayer by a substance injected into the substrate primary interaction between the reactive head groups occurs, followed by solution, *i.e.*, penetration and adlineation, of the tail. In the case of reactants containing two or more reactive head groups it is found that these can associate with head groups

in the monolayer and thus form a series of links. Here another important factor is found operative. If the injected bipolar molecule possess a hydrophobic portion of such a structure that it can pack or adlineate with its neighbors beneath the monolayer, the resultant composite film is remarkably stable. Thus the long chain dibasic acids are adsorbed on to, but do not penetrate monolayers of amines, whilst the diamidines are adsorbed by, but do not penetrate monolayers of cholesterol. Substances containing the phenolic group are of particular interest in this respect as they include a number of biologically important substances. They react with amine groups quite readily and to a less extent with the imido group in a polypeptide chain. Gallic and tannic acids react with great ease with monolayers both of amines and with proteins. It is interesting to note that the reactivity of tannic acid with the spaced amine groups of the protein is high and that subsequent injection of fatty acids beneath such treated monolayers in the dispersion of the galloyl-amine or galloyl-protein complex film, but not in the tanned one—an indication of the effectiveness of the interlinkage produced in the non-dispersible network

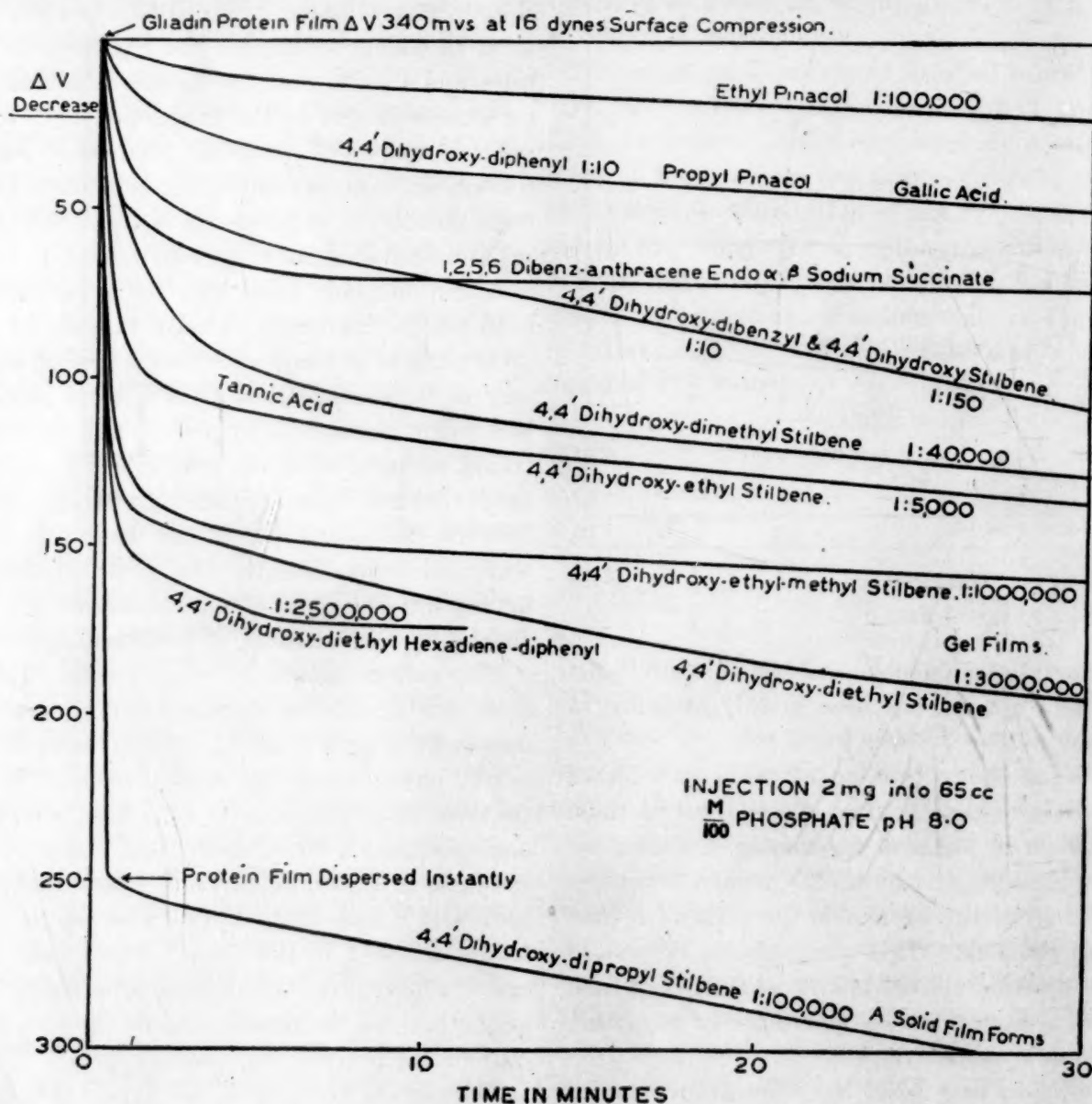


FIG. 3

by the multiple point contact of the large tannic acid molecules.

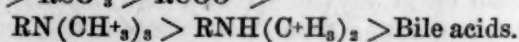
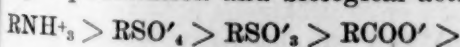
The extremely reactive oestrogenic compounds of Dodds and Lawson, of which the *pp'* dihydroxy diphenyl hexadiene and stilbene derivatives form a definite series in which the ratio of hydrophobic to hydrophilic portion can be varied, present an interesting series, the results of injection of which under a protein monolayer are shown in the attached curve.

It will be noted that reaction sets in rapidly, but equilibrium is only finally attained after some 15 to 20 minutes, and that there is a parallelism between the oestrogenic activity and the protein adsorption except in the first and the last members, points we shall refer to later.

In apparent conformity with Traube's view, there is a marked increase in adsorption with increase in the number of CH_2 groups in the molecule, and this adsorption is cut down by the insertion of polar groups. This effect is clearly exemplified in comparing the diethyl stilbene or dibenzyl compounds with the corresponding pinacols. If, however, reactive polar groups, *e.g.*, the phenolic hydroxyl, had been inserted instead of the primary alcoholic groups in the pinacols, a marked increase rather than a decrease in adsorption would have been observed, for the following compounds react in order of increasing adsorption on both amine and protein monolayers—cresol, gallic acid, digallic acid, purpurogallin and tannic acid. This order is, however, reversed to give a normal Traube series when these substances are injected under a relatively non-reactive monolayer such as a long chain acid.

A wide variety of substances have been examined from this point of view, namely, their extent of interaction with protein monolayers, and it has been found that there is a direct parallelism between their extent of interaction and their lethal action on paramecia. Another significant biological similarity has been noted when we measure the extent of penetration of a series of substances containing identical hydrophobic "tails," *e.g.*, a C_{12} chain but with different head groups, into a monolayer of a typical lipid such as cholesterol. In all cases the extent of interaction as measured by the increase in surface pressure caused by the injection of 0.33 mgm/100 cc under a film of cholesterol originally extended to 40 A^2 per molecule is found to be closely parallel to the hemolytic activities and lethal activities on paramecia of these substances.

These latter can be placed in order both of monolayer penetration and biological activity as follows:



We may conclude that the most reactive group in the protein macromolecule is the amino group, since the $-\text{NH}-\text{CO}-$ group is poorly reactive, a point of

some interest when we examine the reactions of lecithin and of cephalin. This order of head group reactivity receives confirmation when penetration into monolayers containing these head groups is examined, *i.e.*, on inverting the system. When we compare the reactivities of a series of long chain compounds with identical head groups it is found that biological activity and film penetration commences with C_9 when attached to a very reactive head group, with C_{12} when attached to a poorly reactive group, and reaches a maximum value at *ca.* C_{18} . It is interesting to note that it is not necessary for all the carbon atoms to be in the form of a chain but may be enclosed in ring systems; thus activity commences with diphenyl derivatives and increases with addition of carbon atoms to an optimum as in the bile acids, stearic acid, diethyl stilbene and benzpyrene. By examining the reactivity of substances containing two reactive groups at various spacings underneath protein monolayers, it is possible to obtain some idea as to the statistical distribution of the reactive groups in the monolayer. It would appear that some 12.5 \AA is the mean distribution of the amine groups beneath a gliadin film. In the native protein such spacings are naturally different, and thus reactions involving two-point contact will not take place in bulk phase unless the spacing is unaffected by two-dimensional unrolling of the protein.

We have referred to the modification which must be introduced into either the Overton Meyer or Traube concepts of biological activity, *i.e.*, lipid solubility or capillary activity necessitated by the concept of specific head group interaction. We see that a definite limit is also set to the hydrophobic portion of the molecule, not only on account of the decreasing solubility in the aqueous phase causing difficulty in transport and on account of the ease of adlineation or packing having an optimum of C_{18} for association with sterols or fats, but also because a new phenomenon, as exemplified in the figure, sets in with long chains, *viz.*, dispersion of the monolayer, most marked in the case of 4,4'-dihydroxy dipropyl stilbene. It is possible that this phenomenon of film collapse and dispersion may be a generally important factor in setting the upper limit to the chain length or more generally the capillary activity of homogeneous series of biologically important substances, *e.g.*, anesthetics. This dispersion of protein films may have biological counterparts in adsorption on specific portions of the cell surface similar to the hemolytic activity of long chain compounds such as oleic acid, which readily disperses protein films. Another interesting parallelism has been observed in the surface reactivities and oestrogenic powers of two isomeric compounds (*pp'* dihydroxy diethyl dibenzyl), one being markedly differentiated from the other in both protein adsorption and in oestrogenic activity. Here models indicate that the trans arranged

rings can pack laterally with one another in sheet form much more readily and with a greater degree of adlineation than the *cis* structure, imparting stability to the adsorption complex formed with the former substance.

In advancing these somewhat novel principles based upon the hypothesis of a parallelism of film reactions and biological activity, it is desirable to point out exceptions. It is found, for example, that 4,4'-dihydroxy diethyl pinacol is a much more effective estrogenic agent than either its paramecidial activity or adsorption on protein monolayers would suggest. The view might be advanced that on certain living tissues it can be partly converted by enzymitic dehydration to the extremely active 4,4'-dihydroxy diphenyl hexadiene. Another interesting exception is to be found in desoxycholic acid, which is the only hemolytic agent in the bile acid (*ca.* 1:550) series and is likewise lethal on paramecia. It is as we have seen unreactive to films of protein, cholesterol and glycerides, and in fact a specific interaction with fatty acids is involved.

This method of attack permits us to investigate the nature of the coatings of cells or unicellular animals and plants by examining the effects of lipid or protein penetrating substances on them.

Thus both red cells and paramecia are affected by both lipid and protein monolayer penetrating (cytolyzing) or adsorbing (agglutinating) agents, and we deduce that their surface structures must contain lipoproteins or consist of a lipid protein mosaic; whereas certain other unicellular animals frequently found associated with paramecia and in addition the cilia of mytilus are not affected by protein dispersants but are readily influenced by lipid penetrating agents, and their coatings in consequence must be chiefly lipoidal in nature.

Examination of the carcinogenic hydrocarbons by the monolayer technique reveals the interesting fact that whilst they themselves are unreactive they are readily converted into extremely reactive water-soluble photo-oxides. These substances are not only reactive to protein monolayers like the water-soluble dibenzanthracene endosuccinate, but also are paramecidial, the parallelism between the biological activity and monolayer reaction being maintained.

Many attempts have been made to construct model systems to yield potential differences analogous to the bioelectric potentials observed in tissues. The work of Beutner, Bauer, Cremer and others suggests that potential differences of magnitude corresponding to those found in living systems can be obtained by interposing suitable oil phases between electrolytes of different composition, and the fact that the penetration of large molecules into living cells frequently follows

their lipid solubility has given support to the theory that the seat of the bioelectric potential lies in the lipid-like cell wall. The order of thickness of such cell walls can not exceed a few molecular layers, and we must take this fact into consideration. We have noted that at the lipid-water interface there will exist an orientated layer of dipoles, and on placing a monolayer at the interface, the original array of solvent dipoles will be replaced by one consisting of the material of the monolayer. If an electrolyte be brought to equilibrium in both the homogeneous phases, it is clear that opposite the monolayer in both the aqueous phase and in the lipid phase adsorption and electrokinetic potentials² will be built up of such magnitudes that the total potential fall across the interface, which may be written $\xi_{oil} + \Delta V + \xi_{water}$, must be zero. If the lipid phase be replaced by air no diffuse double layer can be built up, since the gaseous ions produced by the usual radioactive source are continually drawn into the liquid phase; there is in consequence a permanent potential fall equal to $\Delta V + \xi_{water}$, which is the one customarily measured.

It is evidence that a bioelectric potential difference may be caused by a sudden alteration in ΔV , for the compensating potential differences ξ_{oil} and ξ_{water} must take time to readjust themselves by diffusion to the new equilibrium values. Since in general the electrolyte concentration in the aqueous phase is high, it seems probable that ξ_{water} will adjust itself to the new value acquired by ΔV as rapidly as ΔV can be caused to change either by mechanical, electrical or chemical means. Thus surges in potential difference across the interface due to a periodic alteration in ΔV may be caused by the slow readjustment of ξ_{oil} , for it is in this phase that the ionic concentration is low.

Another source of biological potentials is to be found in the case where the chemical potential of the electrolyte is not the same in the two phases, bringing into existence a diffusion potential across the interface from source to sink. It is clear that a monolayer can only affect the diffusion potential provided that its permeability to the ions is not only comparable to that of the homogeneous phases on each side, but that it also is not equally permeable to both ions. Experiments have shown that monolayers and even built-up multilayers of considerable thickness of proteins are surprisingly permeable to ions and we must presume that the bioelectric potentials do not involve only a protein membrane between the ionic source and sink.

² Whether adsorption or electrokinetic potentials will be built up in any specific case will depend on whether short or long range forces are involved *i.e.*, on the magnitude and spacing of the dipoles. If the dipole system occurs across a relatively thick multilayer the potentials will be purely electrokinetic.

It thus appears that there is some justification for the assumption that it must be a lipoid or a lipo-protein membrane.

It has been the purpose of this address to re-emphasize the importance of the fundamental concepts introduced by Sir W. Hardy and Dr. I. Langmuir as to the structure of matter in the boundary state. I have attempted to show that there is implicitly contained in the concept of molecular orientation a whole series of properties and events for which there are no analogies in homogeneous bulk phase systems. We note that many of the modes and types of the reactions which can be effected in monolayers, and which can be defined with precision and their mechanism established with a considerable degree of assurance, are unique for such

interphases, but are again observed in living and organized material. It is with this object of ultimate correlation with biological behavior that we have taken up the detailed study of interfacial reactions at Cambridge, and I should like to express my deep indebtedness to my colleague, Dr. J. Schulman, who has been associated with me in this object.

Many "vitalistic" models have been proposed in the past, and whilst it might be correct, although unscientific, to suggest that the ultimate level of integration in living matter is incapable of examination and definition, yet I believe that one is justified in asserting that at least one of the important levels to which due attention must be given for a proper understanding of biological activities is that of the ordered interface.

OBITUARY

THE MAYO BROTHERS AND THEIR CLINIC

THERE was nothing mysterious or supernatural about this twentieth century Lourdes at whose doors incredible numbers of the lame, halt and blind have for years been daily delivered from the ends of the earth. Nothing supernatural—unless possibly the flawless, life-long devotion of two brothers for one another be so regarded. Not since the somewhat mythical attachment of those fifth-century physicians, Cosmos and Damian, both of whom in due time came to be sanctified, has there been anything quite like it.

Rochester, Minnesota, fifty years ago, then scarcely on the map, was a prairie town near the headwaters of the Mississippi where in a humble way, at St. Mary's Hospital, the Clinic had its beginning. It was, to be sure, a Catholic foundation in which Sisters of Mercy doubtless prayed for the recovery of their patients. But it was not primarily for prayer, however efficacious, that the afflicted as by a magnet came to be drawn to that particular shrine.

It was rather the world-wide reputation of two forward-looking men whom I like to remember as they were thirty years and more ago, young and vigorous; each blessed with rare surgical judgment, each with hands which seemed possessed, in an emergency, with an uncanny ability to do, unflustered, just the right thing at the right moment.

At this shrine there was plenty of ritual, to be sure, but it was the ritual of the well-drilled, silent, operating room where for every movement there is a reason; where the incense in the air is not to conceal corruption but to produce painless sleep; where the water in which gloved fingers are dipped is holy only because it is sterile.

Their father, the senior Dr. Mayo, pioneer and Indian fighter, was still alive when I first came to know the place in its early simplicity. There were then but two operating tables, at one of which "Dr. Will" offi-

ciated, at the other in an adjoining room "Dr. Charlie." They were thus affectionately differentiated by every one—staff, patients, employees and fellow townspeople—not to mention the countless visiting doctors who even then were wearing a path to their door.

For these also soon came from all parts of the world, often by special trains, to see for themselves what modern miracles were being performed daily in this once obscure country town. To what they could learn and carry away for their own use they were more than welcome, for our profession has no trade secrets. The more widely knowledge can be disseminated, the better for every one.

And so, as the years slipped rapidly by, a great tower of healing, known everywhere as the Mayo Clinic, was finally erected—a living memorial to a great idea, not a mere place of worship for tradition dead and gone, like the Basilica of SS. Cosmos and Damian built some fifteen centuries ago in Rome by Pope Felix IV.

Another contemporary pair of no less self-effacing brothers—Wilbur and Orville Wright of Dayton, Ohio—were also at about the same time dreaming dreams of a different sort that in no less spectacular fashion came likewise to be fulfilled. Like the Mayos, they seem to have imbibed in their youth the flavor of the old Northwest Territory where the offspring of the early settlers were reared to think more highly of serving mankind than of helping themselves.

One is led to wonder whether imaginative visions of such kind are not more likely to occur and be more possible of realization for those who live where horizons are broad than for those cooped up in metropolitan centers where, even could the rising or the setting sun ever be seen, there would be no time to stop and commune with it.

Different as W. J. and C. H. Mayo were from each other, I have always felt that there was something Lincolnesque about them both. It was shown not only

by their modesty and self-effacement, but in their shrewd appraisal of other people in whatever walk of life and in their quiet dry sense of humor. About this there was nothing boisterous, but I have known them to save with Lincoln-like readiness many an awkward situation by an appropriate story more often turned on themselves than otherwise.

Lincoln of course was pitchforked out of his native environment in the old Northwest into a position of responsibility he could not refuse. So the Mayos were ready to serve when called, as they did during the war; but they very much preferred their own countryside with its comparatively simple life despite the ever-increasing responsibilities and laborious routine of their professional work. They felt only an amused pity for those who thought they were wasting their talents in a small town and who ventured to offer them positions elsewhere of supposedly wider influence.

W. J. once said to me, "When Charlie gets so busy on his farm he forgets to have his shoes cleaned, he takes a night sleeper to Chicago knowing that he will find them well polished under his berth in the morning." Had he been encountered by some traveler on the train who with Mid-West informality asked his occupation, he would have replied, "A Minnesota farmer." Had Dr. Will been similarly asked who he was by some chance companion, he probably would have replied: "I'm C. H. Mayo's elder brother."

After Charlie's death, their friends knew the separation could not be for long. There is a tradition among surgeons that they are likely to meet their end by the same malady in the treatment of which they have themselves specialized. So it was entirely consistent that "Dr. Will" when nearly eighty should calmly submit to an operation whose difficult technique he had not only perfected but countless times had successfully carried out on persons of younger age who still survive to bless him.

The modern world is all too accustomed to gauge success in terms of net income, and thus measured the returns from the Mayo Clinic exceeded the dreams of avarice; but when in 1915 the Mayo Foundation was established Dr. Will simply stated: "We never regarded the money as ours; it came from the people and we believe, my brother and myself, that it should go back to the people."

HARVEY CUSHING

THE SCHOOL OF MEDICINE,
YALE UNIVERSITY

RECENT DEATHS AND MEMORIALS

DR. HENRY SMITH PRITCHETT, president emeritus of the Carnegie Foundation for the Advancement of Teaching, died on August 28 at the age of eighty-two years. Before becoming president of the foundation in 1906, Dr. Pritchett had been professor of astronomy at Washington University, St. Louis; superintendent of the U. S. Coast and Geodetic Survey, and president of the Massachusetts Institute of Technology.

THE death is announced of Professor L. Lévy-Bruhl, professor of philosophy in the Sorbonne from 1899 to 1927, president of the Institut française d'Anthropologie during 1927-30, aged eighty-two years.

The British Medical Journal reports the death of Professor M. B. Krol, director of the clinic for nervous disorders at the All-Union Institute of Experimental Medicine. Born in 1879, Professor Krol was chief physician at the Kremlin Hospital from 1934 to 1938, and in 1935 he was chairman of the Soviet delegation to the second International Neurological Congress in London.

ON the eleventh anniversary of the death of Dr. Hideyo Noguchi, of the Rockefeller Institute for Medical Research, in Accra, West Africa, where he had gone for work with yellow fever, a memorial hall was dedicated at his birthplace in Okinajima, Japan.

SCIENTIFIC EVENTS

MARINE ENGINEERING AT THE MASSACHUSETTS INSTITUTE OF TECHNOLOGY

THE prospect of expansion in naval and merchant ship-building during the next ten years and a demand for naval engineers of exceptional qualifications has led to the establishment at the Massachusetts Institute of Technology of an advanced course in marine engineering. The course will last for one year and will lead to the degree of master of science. While it is designed primarily for graduates of Annapolis, and arranged with the cooperation of the Navy Department, it will be offered also to a group of selected civilian graduate students. It is expected that ten

experienced officers of the United States Navy will be detailed to the institute for this course and that five civilians will be admitted.

The naval building plans call for replacement of a large part of the present fleet, including battleships, cruisers, destroyers, submarines and various service ships, while the Maritime Commission is planning construction of 500 ships for the merchant marine. This program requires engineers with special training in the design and construction of marine propulsion machinery, for the major ships involved in both the Navy and merchant marine programs must be designed to give the utmost in economy of operation and reliable service. The training is designed to prepare engineers

for solution of essential problems of marine engineering, including the use of marine power plants operating at high pressures and temperatures. There is also the problem of the application of Diesel engines with hydraulic, electrical or gear drive, the solution of which involves familiarity with its thermal, metallurgical and mechanical limitations.

The basic objective of the course is to give the student a unified and scientific approach to engineering problems within this field, with special emphasis on investigation of fundamental methods of analysis applied to new problems in marine engineering. Cooperating in the course, in addition to the department of naval architecture and marine engineering, will be the departments of mechanical and electrical engineering. The entire resources of the institute will be available for various aspects of the training.

Professors Evers Burtner, Lawrence B. Chapman, Frank M. Lewis, all members of the staff of the Pratt School of Naval Architecture, will give instruction in advanced marine engineering and mechanical vibration in ships, and Professor Lewis will give special attention to instruction in propeller theory and experimental research in this field. Professor Harold L. Hazen, head of the department of electrical engineering, will have charge of advanced problems in his subject; Professor C. Richard Soderberg, of the department of mechanical engineering, a designer of heavy power machinery, will devote his attention to advanced problems in mechanical engineering; the subject of internal combustion engines, particularly Diesel power plants, will be covered by Professor C. Fayette Taylor, one of the leading authorities in engine design; instruction in heat transfer will be given by Professor William H. McAdams, of the department of chemical engineering.

THE NEW RESEARCH VESSEL OF THE BUREAU OF FISHERIES

AIDED by the commercial fishing industry, the Bureau of Fisheries is about to place in service a first-class research vessel for offshore work in the North Atlantic. Through the cooperative interest of the General Seafoods Corporation of Boston, arrangements are being made for the transfer of the *Harvard*, a 152½-foot trawler, to the Bureau of Fisheries. As soon as the transfer of the vessel has been completed, Public Works Administration funds to the amount of \$125,000, allotted late in June, will be made available for the reconditioning and outfitting of the vessel.

Repairs and alterations to the hull and superstructure and installation of equipment for oceanographic studies and experimental fishing are expected to be completed in time to put the vessel into operation on the fishing grounds next summer. Since the *Albatross II* was taken out of service because of lack of operating

funds in 1932, the Bureau of Fisheries has possessed no ship suitable for use on the fishing banks of the Atlantic.

One of the most important problems to be studied with the aid of the new research facilities will be that of maintaining stocks of fish on the nearer banks, a day's run from the New England ports. Under intensive fishing, supplies of haddock in the Georges Bank area have been so reduced in recent years that it has been necessary for much of the fleet to operate on the distant Nova Scotian banks.

As a result of several years' investigation of the haddock fishery, William C. Herrington, in charge of the biological fishery investigations in the North Atlantic area, last fall announced a theoretical basis for operating the haddock fishery of Georges Bank at a level that would maintain a stable yield and guard against reduction of the basic stock. With the aid of a seagoing research vessel, Mr. Herrington and his staff now expect to determine the actual poundage that represents the optimum yield for the haddock fishery.

The program of investigations to be carried out includes an annual survey of the fishing grounds from Nantucket Shoals to the Laurentian Channel to discover the localities in which the greatest numbers of fish are concentrated.

With gear to be installed in the new vessel, biologists will be able to make a census of young haddock too small to be caught in commercial nets. Experiments will be undertaken with commercial fishing gear to develop and encourage the use of nets of a type that will release undersized fish without loss of marketable sizes.

Fluctuations in the catch of mackerel, which may vary more than 50 per cent. from year to year, have been shown by past investigations of the Bureau of Fisheries to be closely linked with the fate of young mackerel during the first months of their lives. It is now planned to make definite measurements of the effects of oceanic conditions on the survival of the young; and to make annual censuses of the newly hatched and one-year-old mackerel so that it may advise the industry whether to expect good or poor fishing. Cruises are also contemplated to discover the location of schools of adult mackerel in years when they do not congregate in the usual areas, as happened in 1937. Tagging of mackerel will be done at sea to further explore the movements of the fish.

THE ASSOCIATION FOR THE STUDY OF SYSTEMATICS IN RELATION TO GENERAL BIOLOGY

THE Association for the Study of Systematics in Relation to General Biology has issued, according to the *London Times*, a statement in regard to its aims and constitution. Hitherto its constitution has been as

loose as possible, and there has been no subscription. In spite of this, useful work has been done, discussions have been organized in connection with the Zoological Society, the Linnean Society and the British Association, and "The New Systematics," a book of essays on recent progress in taxonomy in relation to other branches of biology, edited by Dr. Julian Huxley, will be published soon by the Oxford University Press.

It has now, however, been decided that, in order that the association may function still more effectively, a regular income is necessary, and a subscription of 5s. a year has been fixed for the first three years. An agreement has been made with the Linnean Society, whereby the association may use the society's rooms for meetings, joint discussions are to be held, and the annual report will appear in the *Proceedings* of the Linnean Society.

The general aim of the association is to remedy the isolation which modern specialization has inevitably created in the various branches of biology. Its objects include the study of the bases and practical aims of taxonomy; the examination of the criteria employed in defining species and other systematic categories; the consideration of modifications of the existing categories in the light of various branches of specialized research; the promotion of research; the investigation of methods of teaching systematics; and the promotion of cooperation between workers in different branches of biology and taxonomic problems. The association plans eventually to produce a uniform series of handbooks on the British fauna and flora.

The chairman of the association is Dr. Julian Huxley; J. S. L. Gilmour is botanical secretary; H. W. Parker, zoological secretary, and Dr. J. Smart, treasurer. The address of the treasurer is care of the British Museum (Natural History), London, S.W. 7.

THE INTERNATIONAL CONGRESS OF GENETICS

BEFORE the opening of the International Congress of Genetics at Edinburgh a special cable to *The New York Times*, signed by Ritchie Calder, reported that Professor N. I. Vavilov, president of the congress, together with fifty of his colleagues had withdrawn from the congress and that Soviet science would not be represented either by a delegation or by individuals. The official explanation, contained in a letter to Professor F. A. E. Crew, secretary-general of the congress, is that the Russians could not participate because the congress should have been held in Moscow instead of Edinburgh.

Mr. Calder wrote that this announcement, which was received on the eve of the congress, came as a complete surprise. Two years ago plans to hold the congress in Moscow were abandoned because of differences and restrictions that foreign geneticists could not

accept. By a decision of the international committee that organizes the congress, the meeting was transferred to Edinburgh, but it was also decided that the president should be Professor Vavilov as arranged and that the Russians should have a dominant part in the proceedings.

Three weeks before the opening, Professor Vavilov, who for eighteen months had been actively participating in the arrangements, discovered that the project for meeting in Moscow had not been "abandoned" but only "postponed" and that the Edinburgh proceedings were therefore out of order.

Russian papers, including the presidential address, had been received and printed. They had to be suppressed and all the program had to be readjusted and reissued to close the fifty gaps caused by this wholesale retreat.

No one, according to the *Times*, seriously accepted the official explanation. It is known that there have been growing differences of opinion among Russian geneticists, and one section is demanding "Marxist genetics." Thus Soviet biology has become involved with ideology.

It is also thought that the turn of international events has had some bearing on the fact that the Russians had not received their passports.

About a quarter of the German geneticists had also withdrawn. Six out of twelve members in the field of human genetics were "unable to attend," but thirty-two were expected to be present at the opening of the Congress. One of the principal papers planned for that day was a study of heredity and environment through identical twins by Professor Fritz Lenz, of Berlin. About twenty Italians were expected to take part. The American contingent numbered 120, and there were large delegations from France, the Netherlands and Scandinavia.

OPENING OF THE INTERNATIONAL CONGRESS FOR MICROBIOLOGY

THE third International Congress for Microbiology opened at the Waldorf-Astoria Hotel, New York City, on September 2. According to the *New York Herald Tribune* many scientific men from abroad who expected to be present were unable to attend and others must return as soon as transportation can be arranged.

Nearly all the forty-two official delegates designated by the German government actually sailed on the Hamburg-American liner *Hansa*, but the boat was recalled to Hamburg. Several official delegates designated by the Italian Government were to have sailed on the Italian liner *Conte di Savoia*, but the sailing was cancelled, and the ship is still in Naples.

Some of those who were unable to attend were already in the service of their governments. Among these is Dr. G. Ramon, director of the Pasteur Insti-

tute in Paris, who was to have headed the French delegation. He is engaged in preparing vaccines and anti-toxins for the French Government. Dr. Pierre Lepine, head of the rabies and virus diseases department of the Pasteur Institute, took his place.

The first general session of the congress on Monday was to have been devoted to addresses by Professor Dr. A. J. Kluyver, of Delft, the Netherlands; Dr. Paul Fildes, of London, and Dr. C. Levaditi, of Paris, and Wednesday's general session to addresses by Professor Dr. Eduard Reichenow, of Hamburg, Germany;

Professor A. Missiroli, of Rome, and Dr. B. O. Dodge, of New York. Of these speakers only Dr. Dodge was able to be present. Mayor F. H. La Guardia and Dr. John L. Rice, commissioner of health, welcomed the delegates at the opening ceremonies at the Waldorf-Astoria. Other speakers included Dr. Thomas M. Rivers, director of the Hospital of the Rockefeller Institute and president of the congress; Sir John C. G. Ledingham, director of the Lister Institute, London, and Dr. Lewis R. Jones, of the University of Wisconsin.

SCIENTIFIC NOTES AND NEWS

THE British Association for the Advancement of Science adjourned on September 1 after meeting for only three days. Before adjournment Sir Richard Gregory, formerly editor of *Nature*, was elected president in succession to Sir Albert Seward.

COLUMBUS ISELIN, 2nd, assistant professor of oceanography at Harvard University, was appointed director of the Woods Hole Oceanographic Institution at the recent annual meeting of the Board of Trustees. He succeeds Dr. Henry B. Bigelow, who was elected president of the corporation in succession to Dr. Frank R. Lillie.

P. H. BATES, chief of the Clay and Silicate Products Division of the National Bureau of Standards, has been awarded the Turner Gold Medal of the American Concrete Institute. The award was made for "contributions to science, direction of research and outstanding leadership in advancing the intelligent utilization of cement and concrete."

At the San Antonio meeting of the American Home Economics Association, Dr. Icie G. Macy-Hoobler, director of the research laboratory of the Children's Fund of Michigan, Detroit, was presented with the 1939 gold medal and the \$1,000 prize of the Borden Company for research achievement in applied nutrition.

PROFESSOR JOSEPH RIGNEY D'AUNOY, who recently resigned as dean of the Medical Center of the Louisiana State University, remaining as professor of pathology and bacteriology, has been decorated with the Order of Commendatore of the Crown of Italy "in recognition of his achievements in the fields of medical research and education."

THE honorary doctorate of the medical faculty of the University of Freiburg/Br. has been conferred on Dr. Eugen Fischer, professor of anthropology at Berlin. He has also been awarded the Goethe prize for art and science.

THE following corresponding members of the Prus-

sian Academy of Sciences have been elected: Dr. Heinrich Vogt, professor of astronomy at Heidelberg; Dr. Peter Adolf Thiessen, professor of physical chemistry at Berlin, and Dr. Siegmund Shumacher, professor of histology and embryology at Innsbruck.

DR. A. FRANKE, of Arnstadt, Germany, has recently received the honorary doctorate of the University of Jena for his contributions to geology, especially in the field of micropaleontology.

At Teachers College, Columbia University, Dr. Jean Broadhurst, professor of bacteriology, and Dr. M. A. Bigelow, professor of biology, have been appointed emeritus professors. Successors have not been appointed because the Division of Practical Science and the Institute of Practical Science Research have been discontinued.

DR. EDGAR HULL, for the past eight years a member of the Medical Center, New Orleans, has been made acting head of the department of medicine of the Louisiana State University. He succeeds the late George S. Bel.

DR. KARL BRANDT, professor of agricultural economics in the Food Research Institute of Stanford University, has joined the staff of the Giannini Foundation of Agricultural Economics of the University of California.

DR. RALPH W. BOST has been made head of the department of chemistry of the University of North Carolina. He takes the place of Dr. Edward Mack, Jr., who resigned to become a member of the staff of the Battelle Memorial Institute, Columbus, Ohio.

DR. NELSON F. MURPHY, of the chemical engineering staff of the General Chemical Company, New York City, has been appointed assistant professor in chemical engineering in the College of Applied Science, Syracuse University.

DR. LLOYD H. DONNELL, of the Goodyear Zeppelin Corporation, has become associate professor of mechanical engineering at the Armour Institute, Chicago.

It is reported in *The Collecting Net* that Dr. William C. Young, assistant professor of biology at Brown University, has been appointed associate professor of primate biology at the Yale University School of Medicine. He will work at the Laboratories of Primate Biology, Orange Park, Fla., and at New Haven, Conn.

DR. HARVEY DIEHL, assistant professor of analytical chemistry at Purdue University, has been appointed to a similar position at the Iowa State College.

THE Anderson Clayton Company of Texas is continuing the support of industrial research fellowships, for the study of industrial utilization of hemi-cellulosic constituents of plants, at the Iowa State College. Professor E. I. Fulmer is director of the research. Dr. John A. Dunning will hold a fellowship for the coming year.

THE *Journal* of the American Medical Association reports that Dr. James R. Martin, chief surgeon at the State Hospital for Crippled Children, Elizabethtown, Pa., and director of the state program for crippled children under the Social Security Act, has been appointed James Edwards professor of orthopedic surgery at Jefferson Medical College, Philadelphia. He succeeds Dr. J. Torrance Rugh, who has resigned after holding the chair since 1918 and who will become professor emeritus.

DR. KENNETH M. SODERSTROM, of Seattle, has been appointed a member of the staff of the division of epidemiology in the Washington State Department of Health in charge of tuberculosis control.

DR. WESLEY COCKER, assistant lecturer in organic chemistry at University College, Exeter, has been appointed lecturer in chemistry at King's College, Newcastle, Durham, in place of Dr. R. D. Haworth, who has been appointed to the chair of chemistry in the University of Sheffield. J. A. Lyddiard, of the Standard Telephones and Cables, Limited, New Southgate, has been appointed to a new lectureship in electrical engineering.

CHANGES in the department of hygiene at the University of California have been announced as follows: Lecturers appointed include Dr. Jacques P. Gray, who has resigned his position as director of public welfare in San Francisco, and Dr. A. Stampar, professor of public health at the State University of Zagreb, formerly director of public health in Yugoslavia and expert in rural health matters for the League of Nations. Dr. Eschscholtzia L. Lucia, associate professor of biometry, has been promoted to a professorship. Dr. Frank L. Kelly, for several years assistant professor of public health administration and now city health officer of Berkeley, will serve as lecturer in public health in the second semester.

O. C. DURHAM, chief botanist of the Abbott Laboratories, Chicago, will make a study of pollen grains in the upper air. The trip by commercial airplane will extend from the Gulf of Mexico to Alaska, across the Atlantic to England and across the Pacific to China. Mr. Durham is continuing the work of Dr. Fred C. Meier, of the Department of Agriculture, and Dr. Earl B. McKinley, dean of the George Washington Medical School, who died in the crash of an airplane in the South Pacific while making aerial studies of the distribution of pollen, spores and disease germs.

THE Swiss Society of Naturalists has announced that the one hundred and twentieth annual meeting will be held at Locarno from September 23 to 25 in conjunction with the Swiss Medico-Biological Society.

THE eighth annual convention of the Biological Photographic Association will be held at the Mellon Institute for Industrial Research, Pittsburgh, from September 14 to 16, under the presidency of Louis Schmidt, of the Rockefeller Institute for Medical Research. There will be a session on the uses of scientific photography at which the speakers will include Robert Cook, Washington, D. C., editor of the *Journal of Heredity*; Watson Davis, director of Science Service, Washington, and David Dietz, science editor of the Scripps-Howard newspapers, Cleveland.

THE department of industrial medicine of the medical school of Northwestern University will hold its third annual symposium on Industrial Disease and Hygiene on September 25 and 26. There will be four sessions presided over by Drs. Merritt Paul Starr and M. Herbert Barker, assistant professors of medicine at the university; Wilber E. Post, clinical professor of medicine, and Edward A. Oliver, associate clinical professor of dermatology, both of Rush Medical College.

AT a meeting held on August 29, the board of directors of the Union Carbide and Carbon Corporation approved an agreement for the acquisition by the corporation of all the assets of the Bakelite Corporation, founded by Dr. L. H. Baekeland over twenty-five years ago. The Carbide Corporation is a producer of chemical raw materials and the Bakelite Corporation a user of chemicals. According to the announcement it is expected that "the coordination of technical knowledge, research, production methods and distribution facilities of these two organizations will result in the improvement of existing products, the development of new plastics and other chemical compounds, and the discovery of new uses for such materials."

It is stated in the *Journal* of the American Medical Association that the Utah State Board of Health with the collaboration of the U. S. Public Health Service

and the Utah Industrial Commission has begun a study of occupational disease under the direction of State Health Commissioner John L. Jones, of Salt Lake City, who has leave of absence for two years. The state legislature has appropriated \$25,000, which will be used for the conduct of the study with a view to developing a permanent occupational disease service. The federal public health service will participate in the first six months of the investigation, the major problems of which will be exposure to silicious dusts and dusts in bituminous coal mines, lead and other metallic dusts and fumes and certain gases. Later, health hazards in other industries will be investigated.

A NEW siderite, or iron meteorite, to be called the Mapleton meteorite, has been acquired by Field Museum of Natural History from Mr. Harvey Meevers, Mapleton, Iowa. This is the first iron meteorite to be reported from that state. Previous to the discovery of this iron, four other meteorites were known from Iowa, three of which were aerolites or stone meteorites, and one a meso-siderite or variety of iron-stone meteorite. No conclusive evidence is at hand regarding the date and time of the fall of the meteorite, which probably does not represent much more than half of the original mass. It weighs 49 kilograms (108 pounds). Its greatest length, breadth and height are $17\frac{1}{2}$ inches, $9\frac{1}{4}$ inches and $6\frac{5}{16}$ inches, respectively.

THE Committee on Sedimentation of the Division of Geology and Geography of the National Research Council has prepared a symposium on recent marine sediments. This consists of thirty-four papers by specialists in different fields of this subject. Emphasis has been placed upon the processes affecting the

deposition of sediments. Because of the bearing of this subject on petroleum geology, the symposium has been published by the American Association of Petroleum Geologists. Dr. Parker D. Trask, associate geologist of the U. S. Geological Survey, became chairman of the committee four years ago. At that time he proposed the assembling in a single volume of the large amount of information that had been obtained in the previous ten or fifteen years by investigators of conditions in the oceanographical, geological, biological and other publications in many parts of the world. This idea received favorable reception, and a book of 740 pages, which is now about ready for distribution, is the result.

The E. W. Scripps, the research vessel of the Scripps Institution of Oceanography of the University of California, sailed from San Diego early in August for a study of ocean currents and undersea strata from San Diego to Santa Barbara. Samples of undersea strata will be taken about thirty miles off shore. Dr. Roger Revelle, member of the institution, is in charge of the cruise. Dr. R. T. Young, physicist of the Worcester Polytechnic Institute, will make a special study of the transmission of light in sea water. *The E. W. Scripps* returned recently after a cruise of 1,200 miles of the Pacific from the Oregon border to Cedros Islands in Mexico. The cruise, which lasted two months, was made in cooperation with the Federal Bureau of Fisheries, which was interested in studying the distribution of sardine eggs off the California coast. General hydrographic conditions were observed at a number of stations from just off shore to as far as 360 miles at sea.

DISCUSSION

THE MODE OF ACTION OF SULFANILAMIDE

DR. PHILIP SHAFFER'S communication on this subject in the issue of *SCIENCE*¹ for June 16 suggests that both the therapeutic and toxic actions of sulfanilamide may be exerted through a "mechanism by which the sterilizing oxidation intensity of molecular oxygen is applied nearly at its maximum to bacteria and unavoidably also to some extent to host cells."

The undersigned are in agreement with this conception to the extent that it indicates a source of sulfanilamide toxicity. They do not find the available evidence compatible with a concept of identity between the mechanisms producing the known toxic and therapeutic effects nor with an explanation of the therapeutic usefulness of sulfanilamide in terms of capacity to act as a reservoir for an intermediate substance of high oxidizing intensity.

¹ P. 547.

The Shaffer premises: Ingested sulfanilamide is assumed to become (1) converted by a process of biologically mediated oxidation into derivatives which act, in turn, as oxidizing agents; (2) producing injuries to the cellular reducing systems; (3) less easily tolerated by the invading pathogen than by the resisting host.

The acting derivatives are assumed to form a reversible electrode couple (as do ferrous and ferric iron) composed of p-hydroxylamino and p-nitroso benzene sulfonamide "or the corresponding semiquinone free radicals."

The cell components mentioned as especially susceptible to injury by this oxidizing combination are: catalase, hemoglobin, glutathione and ascorbic acid. The injuries are presumed to be more readily tolerated by the host than by the invader because of "the relative immunity of host tissues to toxic effects . . . due

to their lower oxygen tension, their higher metabolism and to higher catalase content."

Association of the oxidizing potentialities of the postulated intermediate with the nitroso and not with the hydroxylamine component: Nitrous acid, in the orientation present in p-nitroso benzene sulfonamide, is an effective oxidizing agent, producing damage to the capacity of hemoglobin to transport oxygen and to the capacity of the body to maintain circulation. Hydroxylamine is not an oxidizing agent at the pH of the blood, excepting toward substances of unusually powerful reducing capacity or under conditions of catalytic mediation. *In vitro*, it reduces Fehling's solution much as glucose does. *In vivo*, it becomes converted into nitrite^{2,3}—again acting as a reducing, not an oxidizing agent. The point is emphasized because hydroxylamine is known to block catalase action in concentrations as small as M/100,000.⁴

Insusceptibility of catalase to oxidative injury of the type postulated: The oxidizing potentialities of p-nitroso benzene sulfonamide would be a source of injury to hemoglobin, glutathione and ascorbic acid, but not to catalase. Keilin and Hartree⁵ and K. G. Stern,⁶ authorities on the properties of catalase, report it to be so extraordinarily resistant to oxidation as to suggest that the iron content of that enzyme may be in the ferrie condition, passing fleetingly into the ferrous condition only after reduction by hydrogen peroxide.

Successful chemotherapeutic action is directed against a type of vulnerability, in the pathogen, not shared by the host: Oxidizing actions against hemoglobin, glutathione and ascorbic acid are directed against oxygen-carrying power and against capacity to sustain circulation. They are highly toxic because they strike at the host where he is most vulnerable in his defense against oxygen want. The pathogens responsive to sulfanilamide are less vulnerable to oxygen want⁷ and more vulnerable to peroxide.⁸ The maximum chemotherapeutic possibilities are obviously not to be sought in an action striking at the defenses against oxygen want but in an action striking at the defenses against peroxide, namely, against catalase.^{9,11} For this action, the reducing, hydroxylamine derivative of sulfanilamide is definitely available^{9,11} not the

oxidizing nitroso derivative, which is a source of toxicity.

Alternative suggestion: There can be no question but that p-hydroxylamino and p-nitroso benzene sulfonamide are obtainable from sulfanilamide by biologically feasible types of oxidation. They may not, however, be produced together but, rather, stepwise: the hydroxylamine derivative being formed within the locus of infection^{9,11} by the metabolic process which yields peroxide, and the nitroso derivative being formed following diffusion of the hydroxylamine from the areas vicinal to the cell substance of the pathogen into the blood.

This stepwise production, first of the therapeutically active derivative and, secondly, of the toxic derivative, is possible in the manner outlined. It would not be possible as a result of the peroxide-mediated type of oxidation postulated by Shaffer. The latter type of oxidation is, however, not indicated: (1) because the pathogens most responsive to sulfanilamide are not those producing the most peroxide and permitting accumulation of peroxide to highest levels—as is demanded by a hypothesis of conversion mediated by peroxide—and (2) because such a type of oxidation contains no factor of self-limitation. (Production of active intermediate as a function of available peroxide concentration would increase progressively with increasing peroxide concentration until the pathogen was destroyed. Sulfanilamide does not act, *in vivo*, in any such drastic fashion. It produces only a degree of growth retardation, in infections responsive to its action, sufficient to hold down the numbers of the pathogen to be disposed of, by the host, to levels within possibility of control.^{10,11})

An assumption of stepwise production of the therapeutically active and toxic agents opens up the possibility of using, in place of sulfanilamide, an agent making hydroxylamine available, within the locus of infection, in a form not so readily oxidized to a nitroso acid derivative as is p-hydroxylamino benzene sulfonamide. The comparative anti-catalase and anti-hemoglobin potentialities of hydroxylamine linked to the sulfon group, following blockade of the p-amino group against oxidation, should be explored in this connection.

Adjuvant measures should be taken, during sulfanilamide therapy, to counteract toxic actions on hemoglobin and on circulatory capacity so as to permit full realization of therapeutic effect.^{10,11}

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¹⁰ A. Locke, R. B. Locke, R. J. Bragdon and R. R. Mellon, *SCIENCE*, 86: 228, 1937.

¹¹ A. Locke, E. R. Main and R. R. Mellon, *Jour. Immunol.*, 36: 183, 1939.

² J. W. Mellor, "A Comprehensive Treatise on Inorganic and Theoretical Chemistry," Vol. 8. Longmans-Green, New York, 1928.

³ T. Sollmann, "A Manual of Pharmacology," W. B. Saunders, Philadelphia, 1936, p. 479.

⁴ M. G. Sevag and L. Maiweg, *Biochem. Zeitschr.*, 288: 41, 1936.

⁵ *Proc. Roy. Soc. (London)*, B124: 397, 1938.

⁶ *Jour. Gen. Physiol.*, 20: 631, 1937.

⁷ A. Locke and E. R. Main, *Jour. Infect. Dis.*, 46: 393, 1930.

⁸ J. W. McLeod and J. Gordon, *Jour. Path. Bact.*, 26: 326, 1923.

⁹ A. Locke, E. R. Main and R. R. Mellon, *SCIENCE*, 88: 620, 1938.

RED COLOR IN APPLES¹

In 1936 the authors² published a paper identifying and describing the chemical nature of the red pigment in the Winesap apple, and a few months later Sando³ confirmed these findings with the Stayman and Jonathan varieties. The red pigment of three varieties thus has been shown to be idaein, a glycoside which yields cyanidin and galactose on hydrolysis.

At the time the pigment was identified the work was carried out of the laboratory into the orchard in an effort to study the various factors involved in its formation and, if possible, to influence the color produced in certain varieties of moderate or low color. In the summer of 1936 we were fortunate in finding a substance which seemed to enhance the red color of Stayman, and subsequent work in each succeeding summer has confirmed this result and developed a method of treatment which has been more or less effective in improving the red color of several varieties, including Stayman, Rome, Delicious, McIntosh, Jonathan and others. Under certain conditions even such varieties as Golden Delicious and Grimes Golden, which normally carry little or no blush, were affected by the treatment in such a manner as to increase slightly the amount of blush present on the fruit.

We are now conducting trials for the fourth consecutive season and believe that the tests have gone sufficiently far to indicate the general trend involved and to justify announcement of the method employed. The active agent appears to be the thiocyanate ion applied in combination with any one of a number of substances representing the positive group. The materials are applied in relatively low concentration, as a spray, to the foliage and fruit on the tree during the growing season. Up to this year all treatments have been applied with a hand-sprayer, but at present the university power-spray outfit is being employed on somewhat larger-scale operations than have been tried heretofore. Many important questions remain unanswered and final evaluation of the procedure including practical application, if any, must await future work. This notice is being written to invite the attention of anyone or all interested in the improvement of color in apples.

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A FIRE-FLY "SPINTHARISCOPE"

It must be well known that the lantern of a fire-fly, when held by the fingers, emits irregular flashes.

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Jour. Amer. Chem. Soc., 58: 1511-14, 1936.

flashes from minute point-sources in the lantern which follow the normal flash, the light of which fills the entire lantern. I am wondering, however, if the very astonishing spectacle presented by a fly which has been bitten by a spider has been described. Within a few minutes after a few "nips" have been made by the spider, if the fly is removed from the web, the lantern will be observed to glow with a faint green light which shows the same "shimmering" quality as the radium paint on the dial of a watch. Examination with an ordinary hand magnifying glass, of moderate power, shows the lantern filled with bright points of light, which at first sight appear to be in rapid vibratory motion, and at the end of half an hour we have a seething cauldron of hundreds of bright points, dancing and flashing, and giving an almost perfect picture of a screen of zinc sulphide under a terrific bombardment of "Alpha" particles (spintariscopes). The phenomenon persists with undiminished intensity for 48 hours but finally dies out, the fly apparently having returned to normal. The spintariscopes effect is frequently accompanied by an occasional normal flash, which ceases if the fly is decapitated, though the other effect continues.

The normal flash of the lantern is obviously due to the simultaneous excitation of all the luminous centers by nerve impulses from the brain, but the scintillations persist even after the lantern has been severed from the body. Both types of illumination cease if the fly is placed in a narrow glass tube through which a stream of carbon dioxide is flowing. I have produced the spintariscopes effect by inoculations with 1:1000 solution of snake venom, but in this case the fly did not recover.

Under a microscope, with a low power objective, the individual flashes of green light are seen against a black background and the strong vibratory movement, seen with a hand magnifier, appears to be due chiefly to the quenching of a flash at one point accompanied by the successive flash of a luminous center in its immediate vicinity. My impression is, however, that I have seen single flashes quiver, though in this case it may be merely the spreading of the chemical reaction which produces the light, from one part of a cell to another. The phenomenon, seen with the microscope, is really an amazing sight.

The spiders were, in most cases, small ones found in window webs, with bodies not much larger than a grape-seed, and they usually made their first bites on the leg joints of the fly. The sparkling green flashes appeared first along the upper edge of one or both of the two lanterns, sometimes on one side only. The phenomenon then spread rapidly throughout the entire volume of the lantern. It seems possible that some

³ *Jour. Biol. Chem.*, 117: 45-56, 1937.

information about the nervous system of the fly might be gained by recording the position of points inoculated by the spider and the point or points in the lantern at which the scintillations first appear, but the problem is one for a biologist rather than a physicist.

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THE FIRST ARTICLES ON GROUP THEORY PUBLISHED IN AMERICA

IN 1878 the first volume of the *American Journal of Mathematics* was published under the auspices of the Johns Hopkins University. This volume was edited by J. J. Sylvester (1814-1897) and contains two very short articles written by A. Cayley (1821-1895), who was then professor of mathematics at Cambridge University, England, and one of the most eminent mathematicians in the world. Each of these two articles covers less than three pages, and the former was largely embodied verbatim by its author in a longer article which appeared during the same year in the *Proceedings of the London Mathematical Society*. It contains the absurd statement that there are three groups of order 6, notwithstanding the fact that about twenty-four years earlier A. Cayley stated correctly that there are only two such groups, in the *Philosophical Magazine*, Volume 7, page 40 (1854).

The two articles by A. Cayley to which we called attention in the preceding paragraph seem to be the earliest articles on group theory published on the American Continent, but it is not true that the *American Journal of Mathematics* was the first mathematical journal founded on this continent, as stated by H. Weyl in his "The Classical Groups," page 27 (1939). The most conspicuous exception is *The Analyst*, founded at Des Moines, Iowa, in 1874, which appeared in ten volumes and was noted in the "Jahrbuch über die Fortschritte der Mathematik" for 1875 and later. It contains articles by G. W. Hill, S. Newcomb and other well-known mathematicians of that time and was the forerunner of the *Annals of Mathematics*, which is now published by the Princeton University Press.

The fact that no article on group theory was published in America before 1878 throws much light on the early history of mathematics in our country, since articles on this subject began to appear in Europe about one hundred years earlier and soon attracted

considerable attention on the part of various European mathematicians living in different countries. This interest was greatly stimulated by the work of N. Abel (1802-1829) and E. Galois (1811-1832), both of whom died early but attracted much attention to their tragic lives and fundamental discoveries at an early age. The work of these men was published in Europe about fifty years before work along similar lines was published in America and the latter work had actually been done by a European mathematician who was only published in our country. It took about twenty years more until such work was both accomplished and published in this country.

At present important advances made in Europe attract attention in America so that the slowness with which American mathematicians entered upon the study of group theory is in striking contrast with present conditions and throws light on the isolation of early American mathematicians. Their interests were for a long time practically confined to the writing of elementary text-books which were frequently based largely on the European text-books which had been in great favor but confined themselves to the treatment of elementary mathematical subjects. About half a dozen mathematical periodicals were published in America before the *American Journal of Mathematics* was established, and some of them had contributed by those who resided abroad, but the *American Journal of Mathematics* was the first to publish articles by eminent mathematicians residing abroad.

Just as in the case of the first article on group theory published in America the first text-book on this subject to be thus published was written by a mathematician residing in Europe. This text-book appeared in 1892 under the title "Theory of Substitutions" and was a translation of a work by E. Netto. This was about twenty-two years after a similar work had appeared in Europe under the title "Traité des substitutions," by C. Jordan. Enough may have been said to show how the backwardness of the early mathematics in America is reflected in the history of one advanced subject and to emphasize once more the rapid forward strides made by American mathematicians in recent years. The developments in group theory represent some of the most conspicuous advances, especially in the central and the western parts of our country.

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SCIENTIFIC BOOKS

AN ANECDOTAL HISTORY OF ELECTRICITY

Sparks, Lightning, Cosmic Rays. By DAYTON C. MILLER. ix+192 pp., 183 illustrations. The Macmillan Company, 1939, \$2.50.

THE author describes his book as an anecdotal history of electricity. It is based on the Christmas Lectures for young people by the Franklin Institute in December, 1937. Both the book and the lectures

a natural tribute to the honor of Benjamin Franklin.

The material in the book in the main is objective and is chosen from the highlights of history. The great accomplishments of the human race form easy stepping-stones for the lay reader to reach a fascinating picture of electricity as a part of the world. A museum of electricity outlined from this book would be a grand institution. Not only are abstruse and difficult mathematical derivations omitted, but there is also a minimum of mathematical relationships. Likewise worthy attempts to correlate electrical forces with gravitational forces are not considered.

The first part of the book is designated as "Sparks" or the "Beginnings of Electricity." The illustrations are numerous and in keeping with the writing. Particularly the illustration of "Queen Elizabeth watching Robert's Experiments" is appropriate to an anecdotal account. Perhaps the explanation of the electrophorus could have been improved if attention had been given to the fact that Volta devised it as a voltage multiplier which enabled him to establish the relative values of different metals in the Volta series. Also the reproduction of the scene where Volta was showing the electric Pile to Napoleon Bonaparte would fit. An artist's conception of Madame Galvani discovering the twitching of frog legs when an electrical discharge took place in her kitchen would dramatically mark the invention of the first galvanometer. In the reference to the "attracted disk electrometer" of William Snow Harris and later by Lord Kelvin one may make the valuable implication that the advance in the knowledge of electricity is contingent upon instruments of measurement.

The second part of the book is under the caption, "Lightning," in which simple experiments by Franklin and others lay solid foundation for the science of electricity. Franklin's inspiration for this science was kindled at the age of forty when he saw some experiments by Dr. Spence. Within a year he had well established the theory of positive and negative electricity. Within a few years he experimented in every practicable manner. His procedure was simple and direct, and his interpretation has stood well. He showed that lightning was an electric discharge, and he gave the world an electrostatic motor, the lightning rod, the electric chime and the basis for the "inverse square

law" from the "ice pail experiment" as interpreted by Joseph Priestley. Besides the author presents the versatile Franklin as making contributions to book-printing, flying machines, optics, eye-glasses, chemistry, geology, submarine boats, whirlwinds, stoves, street cleaning, musical instruments, aerial warfare, etc. In reading of Franklin's discussion of science before royalty and the greatest characters of the time, it would seem that as a salesman for science he is a model.

The author quotes Franklin's philosophic attitude, "nor is it of much importance to us to know the manner in which nature executes her laws. It is enough if we know the laws themselves. It is of real use to know that china (ware) left in the air unsupported will fall and break; but how it falls and why it breaks are matters of speculation. It is a pleasure indeed to know them, but we can preserve our china without it. Thus in the present case, to know this power of points (to discharge electricity) may possibly be of use to mankind, though we should never be able to explain it."

The reviewer would like to have seen reproductions of the early precursors of the Vande Graaff electrostatic generator such as were made by Sir William Thomson, Righi or Gray.

The third part of the book treats of modern electrical science up to and including cosmic rays. Maxwell's work is stated necessarily briefly, but the lay reader would hardly suspect him as the greatest intellect of all, whose work guided perhaps more research than any other man. Perhaps if Maxwell's electromagnetic model had been illustrated and explained, the reader might glimpse the great man's plight and vision. Nevertheless, this last part is an excellent short survey and should encourage many to learn more.

A commanding pageant, "Electricity," could be enacted in a three-hour period by selecting characters, apparatus and wording from Dr. Miller's book. Perhaps it would be bold for an ordinary reviewer to suggest that Dr. Miller could direct the staging of a film encompassing the outline and spirit of this book. By such works as these, other men may become inspired by science as Franklin was at forty.

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SPECIAL ARTICLES

ANALYSIS OF SKIN PIGMENT CHANGES AFTER EXPOSURE TO SUNLIGHT

WITH the use of the Hardy recording spectrophotometer and the methods set forth in an earlier paper,¹

E. A. Edwards and S. Q. Duntley, *Am. Jour. Anat.*, 1, 1939.

we have been able to determine objectively the pigmentary changes in the skin after irradiation by sunlight. Here we demonstrate the events following a single one-hour exposure to the mid-day sun (in August, 1938).

A normal male adult served as the subject, and the sacral region was used for the analysis. This area had not previously been exposed to direct sunlight for two years, and it was kept from further exposure after the start of the experiment. Readings were made with diminishing frequency for a total of nine and a half months. The changes following exposure are illustrated by the selected spectrophotometric curves here reproduced (Fig. 1).

The curve made before the exposure (upper curve, Fig. 1) is typical of the sacral region. The blood here is quite venous, as shown by the bluntness of the curve between 500 and 600 millimicrons. Carotene is evidenced by the extremely shallow depression or absorption band at 482 millimicrons, and melanin is moderate in amount as shown by the general upward slope from 400 (violet end) to 700 millimicrons (red end).

Hyperemia was the first effect of the radiation. It was marked in two hours, and maximum in eleven hours. The curve at this time (Fig. 1, lower curve) shows a great lowering in reflectance with pronounced oxyhemoglobin absorption bands, characteristic of an active arterial blood flow (hyperemia). The regression of the hyperemia was rapid in the next few days, and the local blood volume diminished, although it remained distinctly higher than normal. Moreover, there was a shift from oxyhemoglobin to reduced hemoglobin, indicating blood stagnation. This shift could be detected at four days, and is striking in the nineteen-day curve shown in Fig. 1. This curve indicates the gradually decreasing blood volume by the increased reflectance in the region of the twin bands of oxyhemoglobin, while the reduced arterialization is evidenced by the marked blunting of these bands. The venous trend is even more strikingly shown by the fact that despite a diminished blood volume, the nineteen-day curve passes below the eleven-hour curve in the red region of the spectrum (600 to 700 millimicrons). Reference to published curves of reduced and oxyhemoglobin¹ shows that this crossing indicates an increased venous blood content.

During the succeeding months the blood volume slowly receded but did not reach the pre-irradiation level. The shift to a more venous blood continued for four and a half months, after which the blood became fairly constant in its proportions of oxy- to reduced hemoglobin. Thus, while the hyperemia was an acute reaction, the blood stagnation persisted and was still detectable at nine and a half months. This illustrates that solar radiation exerts a long-lasting effect on the blood vessels, a fact previously mentioned by Finsen.²

Since melanin gives no sharply demarcated bands in the visible spectrum, but rather imparts a general

² N. R. Finsen, *Meddelelser fra Finsens Medicinske Lysinstitut*, 1: 6, 1899.

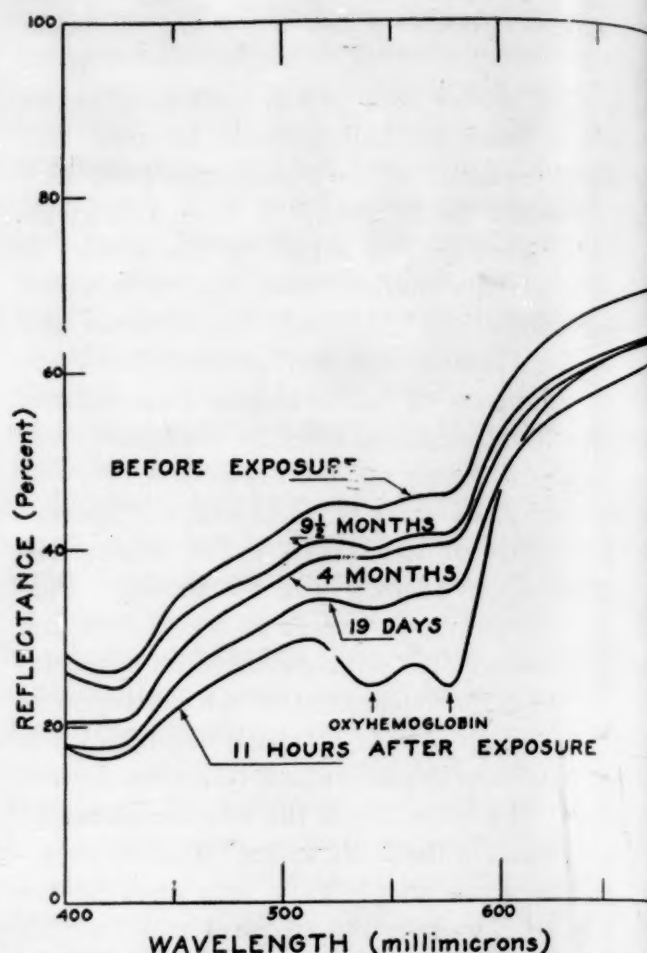


FIG. 1. Spectrophotometric curves of the skin after single exposure to sunlight. Hyperemia (oxyhemoglobin) is maximal at 11 hours, melanin at 19 days, and melanin at four months. Blood stagnation, as registered by reduced hemoglobin, persists from the time of the disappearance of hyperemia for over nine months.

slope to the curve, an increase in this material will be indicated by a depression of the violet end of the spectrum (400 millimicrons). The concomitant effect of the changes in the other pigments must, however, be kept in mind in drawing deductions as to the amount of melanin present. An increase in melanin was apparent in two days, increasing to a maximum on the nineteenth day. The rate of formation of melanin was slowed after this time, and at one month its total quantity also began to diminish. The nine and a half month curve shows the melanin to have returned to approximately the same level as before exposure.

We have previously pointed out that the degeneration of melanin produces an allied pigment which we have named melanoid.¹ The presence of this pigment is shown by a flattening of the spectrophotometric curve near 400 millimicrons. This flattening can be seen in the curve at nineteen days and is maximal at four months, but one fails to find it at nine and a half months. Thus it is seen that the initial appearance of melanoid depends on the formation of considerable melanin. Melanoid increases for some time after the production of new melanin diminishes. Finally, with the disappearance of most of its mother substance, the melanoid ultimately fails to be recognizable.

While carotene showed some fluctuation from time to time, there were no changes in this pigment which could be definitely related to the irradiation.

From the purely physical data represented by spectrophotometric curves, the psychophysical specification of the color stimulus received by the eye of a normal observer was computed³ for I. C. I. Illuminant using data standardized by the International Commission on Illumination in 1931.

	Relative brightness	Dominant wave-length	Excitation purity
	Per cent.	mμ	Per cent.
Before exposure	48.6	580	20.2
11 hours after exposure	31.8	590	20.5
3 hours after exposure	31.8	592	20.9
4 days after exposure	36.9	587	20.7
9 days after exposure	37.4	585	20.7
4 months after exposure	42.6	580	20.5
9 months after exposure	43.6	583	20.1

In this color language "relative brightness" is a measure of the quantity of light reflected by the skin, while "dominant wave-length" and "purity" describe the quality of this light. Thus, hyperemia caused the skin to be much darker and noticeably more red, but it produced only a very slightly more pure or saturated color. At the end of four days the skin was less red but still much darker than normal. This is ascribable not so much to melanin as to the venous stagnation previously referred to. After four months the color of the skin had returned to its original quality, but its brightness was reduced by melanin. The gradual recession of this substance is shown by the increased brightness of the nine and a half months' data. Even at this time the skin was darker than before exposure.

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PRESENCE OF A LEUKOCYTOSIS-PROMOTING FACTOR IN INFLAMMATORY EXUDATES¹

THE recent studies of the writer have indicated the presence of a crystalline nitrogenous substance liberated in areas of acute inflammation, capable *per se* of increasing capillary permeability and of inducing prompt leukocytic migration at the site of injury.^{2, 3, 4} This substance has been termed leukotaxine. Its libera-

³ A. C. Hardy, "Handbook of Colorimetry," Technology Press, Cambridge, 1936.

¹ Aided by grants from the Milton Fund of Harvard University, from the International Cancer Foundation and from the Academy of Arts and Sciences.

² V. Menkin, *Jour. Exp. Med.*, 64: 485, 1936.

³ *Ibid.*, *Jour. Exp. Med.*, 67: 129, 1938.

⁴ *Ibid.*, *Physiol. Rev.*, 18: 366, 1938; *Proc. Soc. Exp. Biol. and Med.*, 40: 103, 1939.

tion and recovery from injured tissue offer a reasonable explanation for two of the basic initial sequences in the development of the acute inflammatory reaction. Leukotaxine has been shown to have no manifest physiological property in common with histamine.^{2, 4, 5}

Leukotaxine, injected either subcutaneously or intravenously, fails to induce an increase in the leukocytic level of the circulation in both the dog and the rabbit. Repeated injections of 30 to 50 milligrams of the material over an interval of several days leave the number of circulating leukocytes essentially unaltered. The independence of the chemotactic factor (leukotaxine) from that concerned with leukocytosis is not wholly surprising when it is recalled that certain inflammatory processes characterized by marked leukocytic infiltration can even be accompanied by distinct leukopenia.

Having apparently eliminated leukotaxine as the factor responsible for the state of leukocytosis accompanying inflammation, studies were undertaken in an endeavor to determine whether the active principle might not be liberated in the exudate as a result of tissue injury. Ponder and MacLeod⁶ recently expressed the opinion that in the blood stream of rabbits with peritonitis the shift to the left of polymorphonuclear counts is probably referable to the absorption of breakdown products of the cells appearing first in the exudate.

Inflammatory exudates were obtained by a variety of methods. In the majority of instances the exudative material resulted from an intrapleural injection of 1.5 cc of turpentine in dogs. Several of the exudates studied, however, were derived either after the intrapleural injection of 0.1 cc 10 per cent. croton oil in olive oil, the combined irritating action of several substances (*e.g.*, magnesium carbonate, staphylococcus aureus toxin and a mixture of aleuronat and colibactragen), or finally by physical injury. The latter consisted in recovering exudative material from a severe burn induced under nembutal anesthesia by scalding the limb of a dog in water heated to about 90° C. The exudate was obtained by removing the edematous subcutaneous tissue, and gently expressing the oozing and abundant exudative fluid content.

From 15 to about 25 cc of whole or cell-free exudate was injected by intracardiac puncture into the circulating blood stream of a normal dog. The results of eighteen such experiments indicate that there is a conspicuous rise in the leukocytic counts several hours after the introduction of an exudate into the blood. The increase in the number of circulating leukocytes averages 70 per cent.

⁵ V. Menkin and M. A. Kadish, *Am. Jour. Physiol.*, 124: 524, 1938.

⁶ E. Ponder and J. MacLeod, *Jour. Exp. Med.*, 67: 839, 1938.

The results of a considerable number of experiments clearly show that the products of injury liberated in an area of acute inflammation are *per se* capable of inducing in a normal dog a prompt leukocytosis to a degree reasonably comparable with that seen in the animal serving as source of the exudative material. Furthermore, some preliminary observations indicate that exudates from animals with marked leukopenia tend to contain a minimal amount of what might now be appropriately termed *leukocytosis-promoting factor*.

The effect on the leukocyte level of a dog manifested by the intravascular injection of an exudate transcends, as a rule, the maximum rise occurring during the rhythmical leukocytic variations. During the period of an experiment, *i.e.*, 6 to 8 hours, the maximum increase in leukocytes of several normal dogs averaged 23.8 per cent. This therefore roughly indicates that there is, as a result of a single injection of exudate, a threefold increase in the number of circulating leukocytes.

To extend the observations, dog serum, sterile broth, large doses of leukotaxine, a broth culture of an exudate and finally a culture of killed *staphylococcus aureus* were injected into the circulating blood of normal animals and of dogs which on other days had received exudates. A leukocytosis invariably failed to develop in these experiments.

For the following reasons it is improbable that the leukocytosis-promoting effect of exudates can be directly referred to the irritant *per se* or any of its derivatives:

(1) Exudates obtained by a variety of unrelated irritants produced in the blood stream an essentially similar effect on the level of circulating leukocytes. Turpentine incubated in serum for varying lengths of time failed to induce a leukocytosis when introduced into the blood stream. These observations, however, do not preclude the possibility that derivatives of turpentine formed in the exudate may still not be responsible for the cellular response. On the other hand, the variety of irritants employed, as well as the fact that a number of unrelated irritating substances fail when injected into the circulation to increase promptly the leukocytic level, suggest that the irritant *per se* bears no direct relation to the leukocytosis-promoting effect of exudates.

(2) The introduction into the circulating blood stream of exudative material obtained as a result of physical injury (*e.g.*, in the form of a severe burn) induces a state of leukocytosis. Such observations clearly indicate that it is unnecessary to refer the leukocytosis-promoting effect of exudate to either the presence of a chemical irritant or any of its derivatives.

The leukocytosis-promoting factor of exudate is

thermolabile. Heating the exudate at 60° C. for several hours inactivates it. It is in large part indiffusible, failing to dialyze through a Cellophane membrane. The effect of the factor seems to be primarily on the bone marrow, producing an outpouring of granulocytes into the circulation. Histamine, adenosine, nucleic acid, all fail to reproduce the same pattern of reaction as does an exudate. The details of all these observations will form the subject of a separate communication to be published elsewhere. Further studies are now in progress in an endeavor to identify the nature of the leukocytosis-promoting factor which seems to offer an explanation for the mechanism of leukocytosis accompanying inflammation.

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GLYCOGEN IN SWEET CORN

It has previously been shown that certain tissue extracts exercise specific effects on the crystallization patterns of cupric chloride, and that the specific oat pattern is dependent on the presence of a polysaccharide in the extract.¹ It has since been found that there is a corresponding polysaccharide in sweet corn, which is essential for the production of the specific corn pattern. This polysaccharide is apparently glycogen.

Though glycogen has been found in a number of lower members of the plant kingdom—yeasts, bacteria, fungi, etc.—it has not previously been reported in any of the higher plants. The designation of a polysaccharide from a plant source as glycogen is rendered uncertain because certain dextrans have properties very similar to those of glycogen. The only striking difference between glycogen and some of the erythro-dextrans is the fact that an aqueous solution of glycogen is opalescent, whereas dextrin solutions are usually clear. Hence it is insufficient to show that a polysaccharide exhibits all the usual characteristics of glycogen, but in addition it must be shown specifically that it is not a dextrin or a mixture of dextrans.

The corn polysaccharide has all the properties commonly associated with glycogen. Its aqueous solution is opalescent, it is resistant to the action of hot alkali, and with acids it is hydrolyzed quantitatively to glucose. Its specific optical rotation is +188° with sodium D light. When iodine is added to its aqueous solution a red-brown color is produced that fades when warmed and reappears when cooled. An erythro-dextrin can be prepared whose properties differ essentially from these only in the lack of opalescence of its solution.

The glycogen and dextrin can be easily differentiated, however, by their effect on the cupric chloride crystal patterns. That of the corn glycogen is totally indis-

¹ Morris and Morris, *Jour. Phys. Chem.*, 43: 623, 1939.

tinguishable from those of the animal glycogens, whereas the dextrin pattern is entirely different.

The action of malt diastase on corn glycogen has been studied, since Glock² has shown that glycogen is hydrolyzed by the diastases at a much slower rate than are the starches. The corn glycogen has been compared with starches, with the erythroextrin mentioned above and with glycogen from other sources. Table 1 shows the fraction of each polysaccharide hydrolyzed after one hour under identical conditions. The amount of hydrolysis was measured by determination of the reduction of the solution by Hanes method³ calculated as maltose.

TABLE 1

Polysaccharide	Source	Per cent. hydrolyzed
Glycogen	<i>Cysticercus fasciolaris</i> ⁴	10
Glycogen	Oyster	15
Glycogen	Yeast	31
Glycogen	Sweet corn	32
Erythroextrin	Corn starch	50
Starch	Rice	60
Starch	Corn	65

It is evident that the corn glycogen is hydrolyzed at a rate much lower than that of the starches, higher than that of the animal glycogens, but nearly identical with that of yeast glycogen.

PREPARATION

The corn is soaked for a day or two, extracted with water, and the extract boiled and filtered. Two volumes of glacial acetic acid are added,⁵ and the precipitated starch either centrifuged or allowed to settle. The acetic acid concentration of the supernatant solution is increased to 75 per cent.,⁶ whereupon the glycogen precipitates. The starch should be redissolved and reprecipitated several times to increase the yield of glycogen, but the separations eventually become less efficient, since both starch and glycogen apparently combine with the acid to form more soluble compounds. Purification of the glycogen can be accomplished by the usual methods.

On one occasion 3.9 gm of glycogen were obtained from 30 gm of Golden Bantam sweet corn. The quantity in one or two kinds of field corn investigated was negligible.

SUMMARY

A polysaccharide apparently identical with glycogen has been extracted from sweet corn.

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SCIENTIFIC APPARATUS AND LABORATORY METHODS

A METHOD FOR THE CONTINUOUS RECORDING OF GASTRIC pH IN SITU

A METHOD has been developed for the determination and the continuous recording of gastric pH *in situ*. To obtain accurate results it was found necessary to keep the silver-silver chloride glass electrode isolated from the gastric mucosa. This was accomplished by a glass or bakelite guard or by a small balloon attached above the electrode. The wire from this electrode was shielded and encased in a Levine tube. In order to mix the gastric contents and to obtain samples another Levine tube was bound to that containing the electrode lead in such a way that the tip of this second tube extended a few centimeters beyond the electrode. With the exception of the opening adjacent to the electrode all other openings of this second tube were covered with balloon rubber. Contact with the saline silver-silver chloride reference electrode was made either on the skin or by means of a thread placed in the aspirating Levine tube. The electrode leads were connected through a Beckman pH meter to a recording potentiometer.

In order to insure accurate recording, certain pre-

² G. E. Glock, *Biochem. Jour.*, 30: 1386, 1936.

³ C. S. Hanes, *Biochem. Jour.*, 23: 99, 1929.

⁴ The cysticercus glycogen was very kindly furnished by Dr. L. Frank Salisbury, of the Department of Chemistry, Yale University.

cautions had to be observed. The exact position of the glass electrode in the stomach was determined by fluoroscopic observation. The gastric contents were constantly mixed by a continuous pump which alternately withdrew and reinjected 25-50 cc of gastric contents at 30-second intervals. By these technical refinements the wide variations reported by Eyerly and Breuhaus¹ between the values obtained by the use of the gastric electrode and those determined on the aspirated speci-

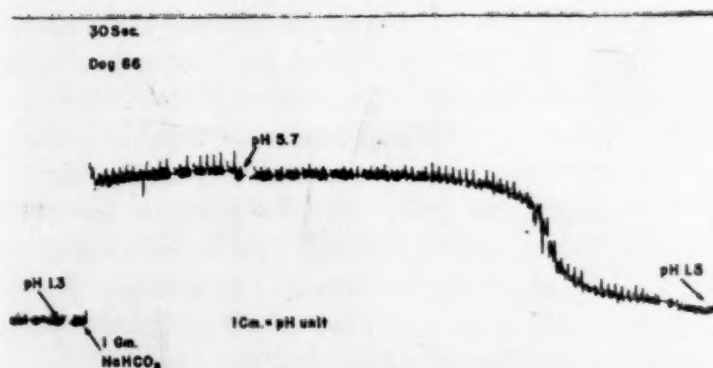


FIG. 1. Changes in gastric pH following administration of 1 gram of sodium bicarbonate in a dog of 17 kilograms, anesthetized with morphine and chloralose.

⁵ Cf., "Methods of Analysis of the Association of Official Agricultural Chemists," Washington, 1935, p. 357.

⁶ Cf. Bell and Young, *Biochem. Jour.*, 28: 882, 1934.

¹ J. B. Eyerly and H. C. Breuhaus, *Am. Jour. Dig. Diseases*, 6: 187, May, 1939.

men were avoided, and the difference in the two types of pH determinations was maintained within 0.5 unit.

The accompanying Fig. 1 shows the accuracy of the method. The fasting contents of an anesthetized dog were diluted to 100 cc with distilled water and a control recording made. The introduction of 1 gram of sodium bicarbonate in 100 cc of distilled water followed by rinsing through the Levine tube with 50 cc of water caused a prompt increase in the pH value. The peak of this rise is conditioned by the pH of the alkaline solution, whereas the plateau level immediately following is the pH of the alkali and gastric content mixture. The duration of the plateau, shown by the gently sloping curve which is terminated by the sudden drop to a low level, is controlled by the amount of alkali added, the rate of acid secretion and the intermittent emptying of the stomach. The amount of emptying can be calculated if the gastric contents are measured after the pH has returned to the low level. By controlling the variables interesting data may be obtained on the efficacy of antacids and the rate of gastric secretion. Information pertaining to these experiments as well as further details concerning the method will be published elsewhere.

We are greatly indebted to Dr. N. R. Trenner for valuable suggestions as well as the construction of the glass electrodes and to Mr. L. Fernandez, who assisted during the earlier part of the experiments.

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CHROMOSOMES FROM LEAVES

A MODIFICATION of Warmke's¹ method for making root-tip smears has been found by the writer to be effective for studying chromosomes in the leaves of certain plants: place young leaves in Carnoy's solution (3 parts chloroform, 2 parts absolute alcohol and 1 part glacial acetic acid) for five or more minutes; transfer momentarily to a solution of equal parts of 95 per cent. alcohol and concentrated hydrochloric acid; put the leaves back into Carnoy's, and, after several minutes, smear in iron aceto-carmine.

By this method the chromosomes of a number of genera have been investigated: *Smilax* L. (Liliaceae), *Sedum* L. (Crassulaceae), *Cercis* L. (Leguminosae), *Punica* L. (Punicaceae), *Sanicula* L. (Umbelliferae), *Pyxidanthera* Michx., *Diapensia* L., *Shortia* Torr. and Gray, *Schizocodon* Sieb. and Zucc., and *Galax* L. (Dia-

¹ H. E. Warmke, *Stain Technology*, 10: 101-103, 1935.

pensiaceae), *Chimaphila* Pursh (Ericaceae), and *Plantago* L. (Plantaginaceae). Metaphase drawings of two species are shown here for purposes of illustration: Fig. 1, *Sedum pusillum* Michx., from Stone Mountain

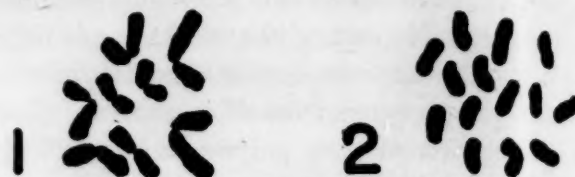


FIG. 1. *Sedum pusillum* Michx., $2n=8$, ca. 3800 \times .

FIG. 2. *Cercis canadensis* L., $2n=14$, ca. 4500 \times .

in Georgia, with 8 somatic chromosomes, the lowest number known for the extremely varied family; and Fig. 2, *Cercis canadensis* L., four trees on the grounds of the College of William and Mary, with 14 somatic chromosomes. Senn² reported a $2n$ -number of 12, n -number of 6, for this species; his drawing of meiotic chromosomes suggests an interpretation of two bivalents in contact to be a single bivalent; his somatic number (not figured) was determined from an anther-wall division. The only other investigated species of *Cercis* has 14 and 7 chromosomes, respectively.³

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² H. A. Senn, *Bibliogr. Genetica*, 12: 175-336, 1938.

³ R. Corti, *Nuovo Giorn. Bot. Ital.*, N. S., 37: 679-690, 1930.

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